

Hawthorn Extract for Treating Chronic Heart Failure: Meta-analysis of Randomized Trials

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The aim of this meta-analysis was to assess the evidence from rigorous clinical trials of the use of hawthorn extract to treat patients with chronic heart failure. We searched the literature using MEDLINE, EMBASE, the Cochrane Library, CINAHL, CISCOP, and AMED. Experts on and manufacturers of commercial preparations containing hawthorn extract were asked to contribute published and unpublished studies. There were no restrictions about the language of publication. Two reviewers independently performed the screening of studies, selection, validation, data extraction, and the assessment of methodological quality. To be included, studies were required to state that they were randomized, double-blind, and placebo controlled, and used hawthorn extract monopreparations. Thirteen trials met all inclusion criteria. In most of the studies, hawthorn was used as an adjunct to conventional treatment. Eight trials including 632 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 (weighted mean difference, 7 Watt; 95% confidence interval [CI]: 3 to 11 Watt; $P < 0.01$; $n = 310$ patients). The pressure–heart rate product also showed a beneficial decrease (weighted mean difference, -20 ; 95% CI: -32 to -8 ; $n = 264$ patients) with hawthorn treatment. Symptoms such as dyspnea and fatigue improved significantly with hawthorn treatment as compared with placebo. Reported adverse events were infrequent, mild, and transient; they included nausea, dizziness, and cardiac and gastrointestinal complaints. In conclusion, these results suggest that there is a significant benefit from hawthorn extract as an adjunctive treatment for chronic heart failure. **Am J Med.** 2003;114:665–674. ©2003 by Excerpta Medica Inc.

Hawthorn extract is among the most popular herbal medicinal products in the United States (1,2), as well as in European countries such as Germany where it is marketed as a prescription medicine (1–3). Preparations usually contain extract derived from *Crataegus monogyna* or *Crataegus laevigata*. The cardiac properties of the extract, which have been investigated in preclinical experiments, suggest positive inotropic and negative chronotropic effects, as well as increases in coronary blood flow (4,5). Clinical studies have reported an increase in exercise tolerance and left ventricular ejection fraction, and improvement in heart failure–related symptoms (6–9).

In most herbal reference texts, hawthorn extract is advocated as an oral treatment option for chronic heart failure (3,10–12). The German Commission E approved the use of extracts of hawthorn leaf with flower for patients with New York Heart Association (NYHA) class II symptoms (13,14). In most countries, preparations containing hawthorn extract are available over-the-counter and

through the Internet. Because the efficacy of hawthorn extract as an adjunctive treatment for chronic heart failure is uncertain, we performed a meta-analysis to assess the evidence from randomized controlled trials.

METHODS

Systematic literature searches were conducted using the data sources MEDLINE, EMBASE, the Cochrane Library, CINAHL, CISCOP, and AMED. The search terms were *hawthorn*, *whitethorn*, *Crataegus*, and *Weissdorn* (common name for hawthorn in German). Each database was searched from its inception until June 2002. Additionally, ten manufacturers of commercial hawthorn preparations and nine experts on the subject were asked to provide published or unpublished trials (15). Hand-searches of relevant medical journals, conference proceedings, and our own files were also performed. The bibliographies of all located papers were searched. No restrictions regarding the language of publication were imposed. Studies published in languages other than English were translated.

To be included, studies were required to state that they were randomized, double-blind, and placebo controlled; used monopreparations of extracts of hawthorn leaf with flower; and included patients with chronic heart failure. Data were extracted systematically for patient character-

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Table 1. Randomized, Placebo-Controlled, Double-blind Trials of Hawthorn Extract for Chronic Heart Failure

First Author (Reference)	Quality Score	Duration	Randomized/ Analyzed (n)	NYHA Class	Preparation	Daily Dose (mg)	Primary Outcome Measures
Tauchert (19)	3*	16 weeks	209/139	III	WS 1442	1800	Max workload (Watt)
						900	Max workload (Watt)
Zapfe (20)	5	12 weeks	40/40	II	WS 1442	240	Max workload (Watt) [†] Exercise tolerance (Watt min) Pressure-heart rate product [‡]
Weikl (21)	4	8 weeks	136/129	II	WS 1442	160	Pressure-heart rate product [‡]
Bödiger (22)	5	4 weeks	85/73	II	LI 132	300	Max workload (Watt)
Leuchtgens (23)	2	8 weeks	30/30	II	WS 1442	160	Pressure-heart rate product [‡]
O'Connolly (24)	3 [§]	6 weeks	36/31	I to II	WS 1442	180	Pressure-heart rate product [‡]
O'Connolly (25)	3 [§]	6 weeks	36/34	I to II	WS 1442	180	Pressure-heart rate product [‡]
Hanak (26)	3	3 weeks	60/58	I to II	WS 1442	180	Max workload (Watt) [†]
							Exercise tolerance (Watt min)

* Three parallel groups.

† Unpublished; data provided by the manufacturer.

‡ Measured in units of systolic blood pressure (mm Hg) × heart rate per minute ÷ 100.

§ Crossover trial.

ACE = angiotensin-converting enzyme; max = maximal; NYHA = New York Heart Association; W = Watt.

istics, interventions, and results. If information was insufficient, we contacted the authors and the manufacturer of the preparation. Methodological quality was

evaluated using the system developed by Jadad (16), which quantifies the likelihood of bias inherent in the trials based on the description of randomization, blind-

Table 1. Continued

Exercise Protocol	Baseline Values		Final Values		Mean Difference (95% Confidence Interval)	Concomitant Medication	Adverse Events in Hawthorn Group (Cases)
	Hawthorn/Placebo	Placebo/Hawthorn	Hawthorn/Placebo	Placebo/Hawthorn			
	Mean \pm SD						
25-W increase/ 2 min to stop	55 \pm 14/54 \pm 15	65 \pm 15/58 \pm 17	5(-0.3 to 10)	Triamterene, hydrochlorothiazide	Dizziness/vertigo (4), bronchitis (4), back pain (5), flu-like syndrome (4), headache (2), arthritis (1), flatulence (1), gastroenteritis (1); dropout due to adverse events (2)		
25-W increase/ 2 min to stop	53 \pm 15/54 \pm 15	58 \pm 15/58 \pm 17	0.3(-5 to 5)				
25-W increase/ 2 min to stop	87 \pm 26/86 \pm 30	93 \pm 23/78 \pm 28	14(2 to 26)	Not specified;	None		
25-W increase/ 2 min to stop	616 \pm 337/624 \pm 391	683 \pm 302/528 \pm 345	162(-72 to 397)	glycosides, diuretics, calcium antagonists, ACE inhibitors and other hawthorn preparations were not allowed			
2 min at 50W	54 \pm 43/48 \pm 30	39 \pm 29/47 \pm 23	-13(-35 to 9)				
2 min at 50W	67 \pm 33/64 \pm 33	61 \pm 29/68 \pm 38	-10(-22 to 3)	Calcium antagonists, ACE inhibitors	Dyspnea, restlessness (1), stomach complaints (1), tachycardia, dizziness (1)		
25-W increase/ 2 min to stop	93 \pm 29/97 \pm 28	108 \pm 36/106 \pm 31	7(-9 to 22)	Diuretics	Migraine, nausea, flatulence (1), palpitations (1)		
2 min at 50W	37 \pm 13/36 \pm 9	27 \pm 13/34 \pm 7	-8(-17 to 0)	Not specified	None		
2 min at 50W	142 \pm 27/148 \pm 29	113 \pm 23/155 \pm 27	-36(-51 to -22)	Lipid-lowering drugs, cough and blood pressure medication, antidiabetics, diuretics, antirheumatics, enzymes	Dizziness (3)		
2 min at 50W	143 \pm 21/158 \pm 20	121 \pm 21/166 \pm 17	-31(-41 to -20)	Not specified;	None		
25-W increase/ 2 min to stop	88 \pm 24/102 \pm 29	98 \pm 22/101 \pm 31	11(-2 to 23)	psychoactive, medication and circulatory active- medication were not allowed			
25-W increase/ 2 min to stop	404 \pm 179/550 \pm 254	504 \pm 200/549 \pm 307	102(-34 to 238)	Not specified;	Not reported		
25-W increase/ 2 min to stop				circulatory active- medication was not allowed			

ing, and withdrawals. The screening and selection of studies, data extraction, validation, and the assessment of methodological quality were performed independently by two reviewers (MHP, KS). Disagreements in the evaluation of individual trials were largely due to errors in reading and were resolved through discussion.

The mean change in maximal workload, as compared with baseline, was defined as the primary endpoint to

assess the difference between the hawthorn and the placebo groups. Weighted means and 95% confidence intervals were calculated using standard meta-analysis software (RevMan 4.1; Update Software Ltd., Oxford, England), which uses the inverse of the variance to assign a weight to the mean of the within-study treatment effect. For most studies, however, the information was insufficient to allow us to calculate the variance of the pre-inter-

vention to postintervention change. The Cochrane Collaboration suggests imputing the variance of the change by assuming a correlation factor of 0.4 between pre-intervention and postintervention values (17). The variance of the change was imputed using this correlation factor and then used to assign a weight to the mean of the within-study treatment effect. Summary estimates of the treatment effect were calculated using a random-effects model. The chi-squared test for heterogeneity was performed to test whether the distribution of the results was compatible with the assumption that intertrial differences were attributable to chance alone. Publication bias was assessed using a funnel plot.

RESULTS

The literature searches identified 26 potentially relevant trials (6,18–42), including one unpublished study (18). Thirteen publications were excluded because they were not randomized and placebo controlled (27–32), did not use monopreparations of extracts of hawthorn leaf with flower (33–36), assessed healthy volunteers (37), were published in duplicate (38), or did not include results (39). Eight trials met the inclusion criteria and provided data for meta-analysis (Table 1). Five other trials were included, but reported data that were not suitable for statistical pooling (Table 2). The flowchart provides an overview of all included and excluded trials (Figure 1). 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 categorize patients.

Four studies (n = 310 patients) measured changes in maximal workload (Figure 2). The meta-analysis indicates a significant increase in maximal workload in patients receiving hawthorn extract compared with patients receiving placebo (weighted mean difference, 7 Watt; 95% confidence interval [CI]: 3 to 11 Watt; $P < 0.01$). There was no evidence of heterogeneity among the studies ($P = 0.5$). 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 3) shows that studies with a smaller sample were distributed further away from the weighted mean difference of all trials, 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 tested whether including only the data from patients treated with the low-dose regimen (900 mg) instead of the high-dose regimen (1800 mg) in the study by Tauchert (19) would alter the direction of the overall result. The meta-analysis of these data was similar to the overall results (weighted mean difference, 6 Watt; 95% CI: –1 to 14 Watt; n = 311 patients).

Other sensitivity analyses assessed trials in which hawthorn extract was administered in addition to other medications (5 Watt; 95% CI: 0.2 to 10 Watt; n = 212 patients) and trials in which it is unclear whether the patients received any other medications (12 Watt; 95% CI: 4 to 21 Watt; n = 98 patients).

Additional outcome data were available in six other trials (20,21,23–26) for the pressure–heart rate product (systolic blood pressure in mm Hg \times heart rate per minute \div 100) and exercise tolerance (Table 1). The meta-analysis of these data suggests a significant beneficial effect of hawthorn to reduce the pressure–heart rate product (weighted mean difference, –20; 95% CI: –32 to –8; n = 264 patients) and a marginally nonsignificant effect on exercise tolerance (weighted mean difference, 117 Watt min; 95% CI: –1 to 235 Watt min; n = 98 patients).

Patients receiving hawthorn extract had an improvement in symptoms such as dyspnea and fatigue (19,22,40,42). The symptom score developed by von Zerssen (43) was used in two trials (19,23). These data suggest a significant differential effect in favor of hawthorn extract (weighted mean difference, –6; 95% CI: –9 to –2; n = 169 patients).

The daily dose of hawthorn extract was between 160 mg and 1800 mg. All trials administered standardized hawthorn extracts. Seven of eight trials used hawthorn extract WS 1442, which is standardized to 18.8% oligomeric procyanidins. The most common adverse event was dizziness/vertigo (n = 8). Five trials reported no adverse events in patients receiving hawthorn (Tables 1 and 2).

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 eight of the 13 trials, most patients were also treated with conventional medications, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, and calcium antagonists (Tables 1 and 2). 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 (44,45). Weight control, dietary measures, smoking cessation,

Table 2. Randomized, Placebo-Controlled, Double-blind Trials Lacking Data for Meta-analysis

First Author (Reference)	Quality Score	Duration	Randomized/ Analyzed (n)	NYHA Class	Preparation	Daily Dose (mg)	Primary Outcome Measures	Exercise Protocol	Main Result	Concomitant Medication	Adverse Events in Hawthorn Group (Cases)
Eichstädt (6)	3	4 weeks	40/40	II	WS 1442	480	Left ventricular ejection fraction	Increase until maximal workload	Significant differential effect	Aspirin, nitrates, calcium antagonists, antidiabetics, lipid-lowering medication, ACE inhibitors	None
Alexander (18)	4	4, 8 weeks	73/73	II	WS 1442	900	Exercise tolerance Pressure-heart rate product	At 65% of maximal workload	No differential effects	Diuretics	Nervousness (1), heart pain (2), sleeplessness (2), hand tremor (1)
Schmidt (40)	5	8 weeks	78/70	II	LI 132	600	Maximal workload Pressure-heart rate product	25-W increase/ 3 min to stop Change from rest to 'under load'	Significant differential effect for both endpoints	Diuretics	Nausea(1), cardiac complaints (1)
Förster (41)	5	8 weeks	72/69	II	LI 132	900	Exercise tolerance	At 65% of maximal workload	No differential effect	Diuretics	None
Iwamoto (42)	4	6 weeks	102/80	II, III	WS 1442	180 to 270	Pressure-heart rate product Symptoms	At rest	Significant differential effect for both endpoints	Not specified; glycosides, dilatatory and antiarrhythmic medication, antihypertensives, and diuretics were not allowed	Nausea (1)

ACE = angiotensin-converting enzyme; NYHA = New York Heart Association; W = Watt.

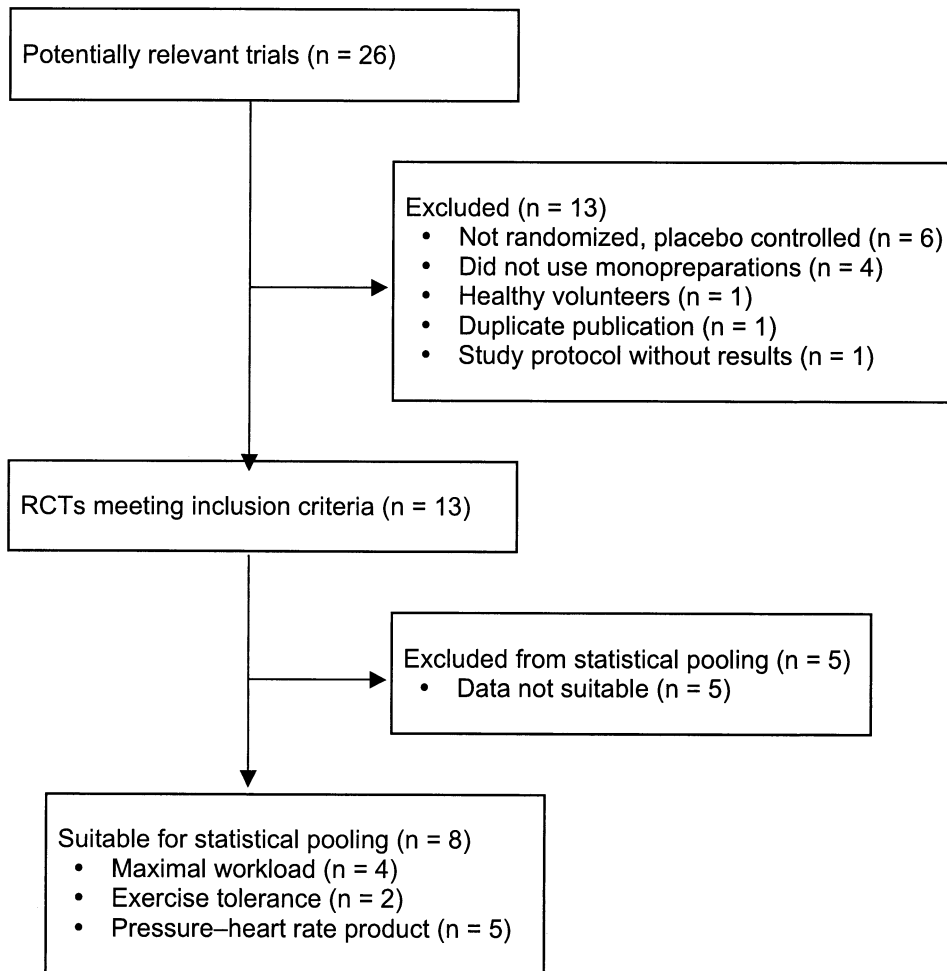


Figure 1. Flowchart.

and pharmacological interventions are generally regarded as first-line treatment approaches for most patients (44,46,47). Diuretics and digoxin lead to an improvement of heart failure–related symptoms, whereas beta-blockers and ACE inhibitors also improve survival (48–50). Angiotensin-converting enzyme inhibitors have been reported to increase parameters of physical performance, such as exercise tolerance, by approximately 20% (51). 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 (52). 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 (29), both groups increased their maximal workload significantly, without differences between the two treatments. Although these data seem encouraging, changes in physical performance due to drug effects do not correlate well with changes in mortality (53). A large-scale study is under way; it compares 900 mg

of standardized hawthorn extract WS 1442 with placebo and will assess cardiac death, nonfatal myocardial infarction, and hospitalization during a 24-month treatment period (39).

Hawthorn extract has positive inotropic effects, decreases atrioventricular conduction time, and increases coronary blood flow. These effects are similar to those of phosphodiesterase inhibitors such as amrinone and milrinone. Hawthorn extract, however, increases the refractory period (54), which may explain why it seems to be associated with antiarrhythmic activity (4,5), whereas phosphodiesterase inhibitors and most other inotropic agents have proarrhythmic effects. Hawthorn extract blocks repolarizing potassium currents in ventricular myocytes, an effect that is similar to the action of class III antiarrhythmic drugs (55). In addition, the positive inotropic effect is similar to the action of cardiac glycosides (56). 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 (39).

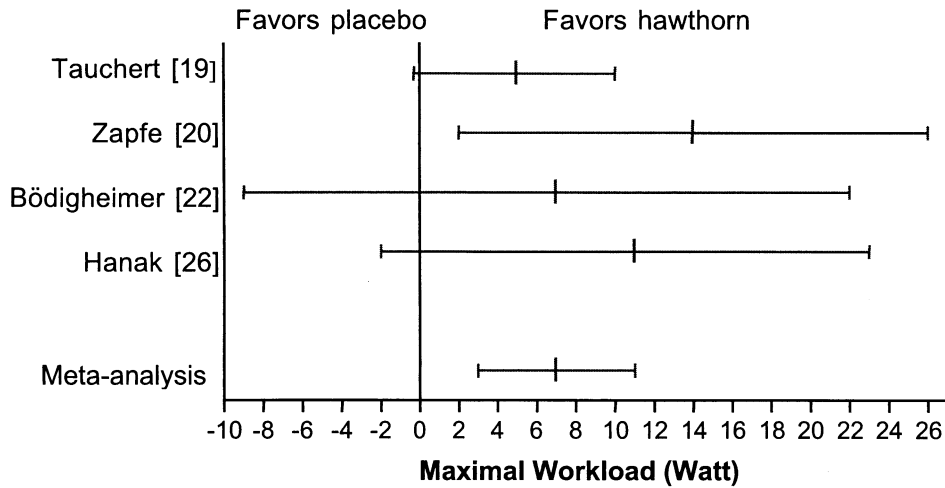


Figure 2. Effects of hawthorn extract for chronic heart failure (random-effects model). The mean differences in the change from baseline are given with 95% confidence intervals. The vertical line represents no difference between hawthorn extract and placebo.

The pharmacologic profile of hawthorn is similar to digoxin, another plant-based option for chronic heart failure (54). 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 (44,57). In contrast, hawthorn extract has a wide therapeutic window. Patients with NYHA class III were treated with 1800 mg of hawthorn extract daily for

16 weeks (19), 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.

Postmarketing surveillance studies report only mild and infrequent adverse events in patients receiving hawthorn extract. In a study of 1011 patients, 14 adverse

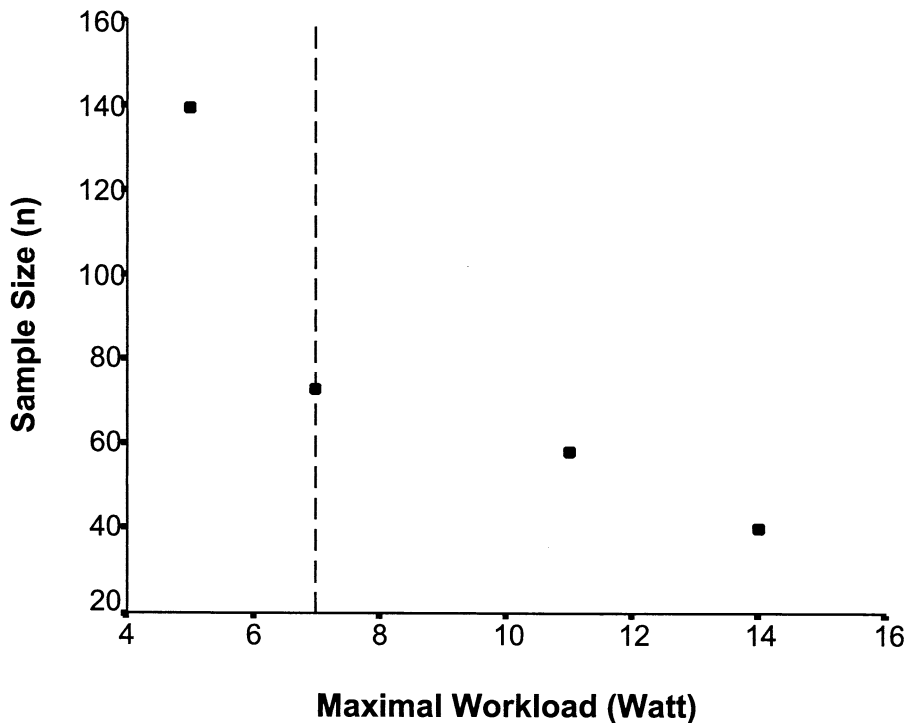


Figure 3. Funnel plot of the mean difference in maximal workload in trials of hawthorn extract for chronic heart failure, plotted against sample size. The vertical line indicates the weighted mean difference of all trials.

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 (58). In another postmarketing surveillance study of 3664 patients who were treated with 900 mg of hawthorn extract for 8 weeks (59), 48 patients (1.3%) reported adverse events, including hot flushes, stomach complaints, palpitations, dizziness, dyspnea, 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 (60,61). Based primarily on animal experiments, hawthorn extracts may interact with anticoagulants, antihypertensives, and cardiac glycosides (62,63). In a preliminary report presented in abstract form, there was no interaction between hawthorn extract and digoxin in healthy volunteers (64). Nevertheless, we believe that hawthorn extracts are not ideal candidates for the over-the-counter market.

Although we attempted to locate and retrieve all trials on the subject, it is conceivable that some were not uncovered. Indeed, 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 (65–67). This includes suggestions that positive findings may be overrepresented in complementary medicine journals (68,69) and that these journals favor positive conclusions at the expense of methodological quality (70). In addition, there is evidence that positive findings tend to be published in English-language journals (71), whereas some European journals are not indexed in major medical databases (72). 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 minimized bias.

We only included data from clinical trials that were randomized, double-blind, and placebo controlled. Nevertheless, the extent of methodological rigor varied among trials. Two studies (20,22) scored the maximum, and one (23) scored as low as two of a possible five points.

In conclusion, 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. Whether hawthorn extract affects the prognosis of patients with chronic heart failure is under investigation.

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