REVIEW ARTICLE

Drug Safety 2006; 29 (6): 523-535
0114-5916/06/0006-0523/$39.95/0



# Adverse-Event Profile of *Crataegus* Spp.
## A Systematic Review

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## Abstract

*Crataegus* spp. (hawthorn) monopreparations are predominantly used for treating congestive heart failure. The effectiveness of hawthorn preparations (flowers with leaves; berries) is documented in a number of clinical studies, reviews and meta-analyses. The aim of this article is to assess the safety data of all available human studies on hawthorn monopreparations.

Systematic searches were conducted on MEDLINE, EMBASE, AMED, The Cochrane Library, the UK National Research Register and the US ClinicalTrials.gov (up to January 2005). Data were requested from the spontaneous reporting scheme of the WHO. Hand searches were also conducted in a sample of relevant medical journals, conference proceedings, reference lists of identified articles and our own files. Eight manufacturers of hawthorn-containing preparations were contacted and asked to supply any information on adverse events or drug interactions. Data from all clinical studies and reports were assessed. Only human studies on monopreparations were included. Data from hawthorn-containing combination preparations and homeopathic preparations were excluded. All studies were read and evaluated by one reviewer and independently verified by at least one additional reviewer.

Twenty-nine clinical studies were identified, of which 24 met our inclusion criteria. A total of 7311 patients were enrolled, and data from 5577 patients were

available for analysis. The daily dose and duration of treatment with hawthorn monopreparations ranged from 160 to 1800mg and from 3 to 24 weeks, respectively. The extracts most used in the clinical trials were WS 1442 (extract of hawthorn standardised to 18.75% oligomeric procyanidins) and LI 132 (extract of hawthorn standardised to 2.25% flavonoids). Overall, 166 adverse events were reported. Most of these adverse events were, in general, mild to moderate; eight severe adverse events have been reported with the LI 132 extract. The most frequent adverse events were dizziness/vertigo (n = 15), gastrointestinal complaints (n = 24), headache (n = 9), migraine (n = 8) and palpitation (n = 11). The WHO spontaneous reporting scheme received 18 case reports. In the identified trials, the most frequent adverse events were dizziness (n = 6), nausea (n = 5), fall (n = 2), gastrointestinal haemorrhage (n = 2), circulation failure (n = 2) and erythematous rash (n = 2). There were no reports of drug interactions.

In conclusion, all data reviewed in this article seem to indicate that hawthorn is well tolerated even if some severe adverse events were reported; this suggests that further studies are needed to better assess the safety of hawthorn-containing preparations. Moreover, the unsupervised use of this drug can be associated with problems, especially if given with concomitant medications.

Approximately 280 species of *Crataegus* (hawthorn) exist, but the ones most commonly used in Western medicine are *C. laevigata* (Poir.) and *C. monogyna* Jacq. The herb is a popular cardiac medication, particularly in Germany, but is also used to treat stomach complaints in China. Preparations containing hawthorn fruits are indicated for stimulating digestion and treating diarrhoea, and for epigastric and abdominal pain.[1] Traditionally, Native Americans used hawthorn berries as a diuretic for kidney and bladder disorders and to treat stomach ache, stimulate appetite and improve circulation.[2] In the UK, hawthorn is used for several cardiovascular complaints, including myocardial dysfunction, hypertension, atherosclerosis and peripheral vasodilation, and as a cardiac antiarrhythmic agent.[3] Today hawthorn is predominantly used as an adjunctive treatment for congestive heart failure. The revised monograph of the German Commission E approved the use of hawthorn leaves with flowers in the treatment of chronic heart failure stages I–II of the New York Heart Association (NYHA).[4]

The constituents of the drug are flavonoids (flavonol and flavones), oligomeric proanthocyanidins, tyramine and tannins.[5] The flavonoids and the oligomeric procyanidins are considered to be the constituents that are largely responsible for the pharmacological actions of the drug. The primary flavonoids are quercetin-3D-galattoside, vitexin-2O-rhamnoside and acetylvitexin-2-O-rhamnoside.[6] The oligomeric proanthocyanidins with a low degree of polymerisation appear to be more active than those with a high degree of polymerisation; the former are more abundant in extracts of leaves and flowers.[7]

The authenticity of a hawthorn preparation is often measured by its content of flavonoids and oligomeric proanthocyanidins. The daily dose tested in clinical trials is 160–1800mg of standardised extract containing 2.2% flavonoids or 18.75% oligomeric proanthocyanidins.[1]

Several *in vivo* and *in vitro* studies have shown hawthorn to have a variety of pharmacological actions: it increases coronary and myocardial circulation, improves myocardial contractility, increases myocardial tolerance to oxygen deficiency and increases cardiac performance.[8] The increase of coronary circulation seems to be due to the inhibition of phosphodiesterase activity with subsequent inhibition of cyclic adenosine monophosphate (cAMP). The improvement in myocardial contractility is based on different mechanisms than that caused by

 

digitalis glucosides; the latter act on the contractile system of the myocardium, whereas hawthorn seems to act through myocardial energy metabolism.[9] This could explain why hawthorn needs more time than digitalis glucosides to exert its action.[4]

Antiarrhythmic, hypotensive, hypolipidaemic and antioxidative activities have also been reported.[1,10,11]

The effectiveness of hawthorn therapy for chronic heart failure is documented in a number of clinical studies, reviews and meta-analyses.[1,10,12] No systematic review on adverse events and drug interactions associated with hawthorn is currently available. Therefore, we conducted this systematic review to assess all available human safety data of hawthorn monopreparations.

## 1. Literature Search Methodology

The following databases were searched from their date of inception: MEDLINE (1951–January 2005), EMBASE (1974–March 2005), AMED (1985–March 2005), The Cochrane Library (issue 1, 2005), the UK National Research Register (http://www.update-software.com/projects/nrr/; search date 20 January 2005) and the US ClinicalTrials.gov website (http://clinicaltrials.gov/; search date 20 January 2005). Data were also requested from the spontaneous reporting scheme of the WHO Collaborating Centre for International Drug Monitoring (https://websearch.who-umc.org/login.asp; search date 25 January 2005).

The search terms were 'hawthorn', 'crataegus', 'whitethorn' and 'weissdorn'. No language restrictions were imposed. To identify additional published or unpublished material, we conducted hand searches of our own files and of a sample of relevant medical journals (*Erfahrungsheilkunde* 1996–2005, *Forschende Komplementârmedizin Klassische Naturheilkunde* 1995–2005, *Phytomedicine* 1995–2005, *Alternative and Complementary Therapies* 1995–2005) and conference proceedings (*FACT – Focus on Alternative and Complementary Therapies* 1996–2005). Further relevant articles were located by hand searching the reference lists of all articles and searching our own collection of articles. Eight manufacturers of hawthorn preparations, identified from standard reference texts,[13] were contacted and asked to supply any information on adverse events or drug interactions related to the use of hawthorn.

Safety data from all clinical studies and reports were assessed. To be included, studies were required to assess monopreparations of hawthorn. Only human studies were included. Data from hawthorn-containing combination preparations and homeopathic preparations were excluded. In the case of duplicate publications, only one report (the more detailed) was included. All sources of information obtained were read and evaluated by one reviewer and independently verified by at least one additional reviewer. Data were extracted according to predefined criteria (patient population, preparation and dose, number and type of adverse events reported). There was no formal assessment of the statistics of the primary data.

## 2. Data from Clinical Trials

The literature search identified 29 articles relevant to clinical trials involving hawthorn preparation. One of these was excluded because it was a duplicate publication and four because they were not conducted using hawthorn monopreparations. The remaining 24 articles were included in this review. We identified 19 randomised clinical trials, two uncontrolled studies, two observational studies and one cohort study (figure 1). In these studies, a total of 7311 patients were enrolled and data from 5577 patients were available for analysis.

In 14 studies, the hawthorn extract used was crataegus extract WS 1442 (dry extract from hawthorn leaves and flowers, standardised to 18.75% oligomeric procyanidins; dry extract ratio 4–6.1 : 1 w/w; the extraction solvent used was 45% ethanol; manufactured by Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany). In seven studies, crataegus extract LI 132 was used (extract of hawthorn leaves and flowers, standardised to 2.25% flavonoids; dry extract ratio 4–7 : 1 w/w; manufactured by Lichtwer Pharma GmbH, Berlin,

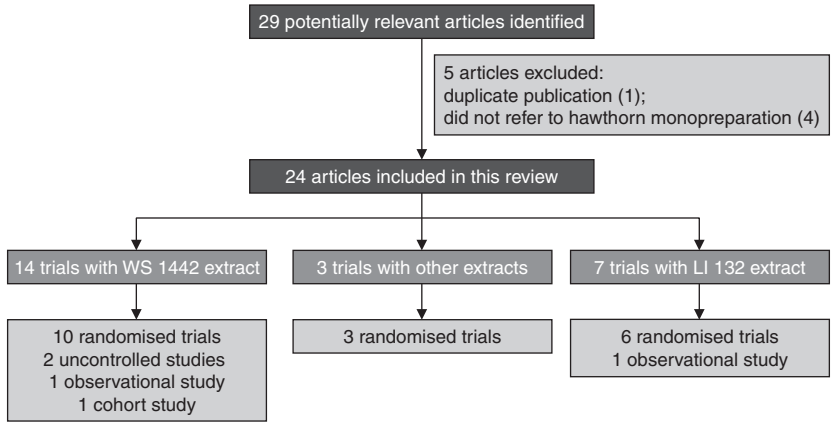


**Fig. 1.** Flow chart of data selection.

Germany). Other extracts were used in three additional studies that are shown in table I. The daily dose administered in the reviewed studies ranged between 160 and 1800mg. The duration of the trials varied from 3 to 24 weeks. The only identified cohort study lasted 2 years.

### 2.1 Clinical Studies with Crataegus Extract WS 1442

Of 14 trials performed with WS 1442, ten were randomised clinical trials,[14-23] two were uncontrolled studies,[24,25] one was an observational study[26] and one was a cohort study[27] (table I).

In these studies, the indication for WS 1442 treatment was chronic heart failure NYHA class I–II (in eight randomised clinical trials,[14-21] the observational study,[26] the cohort study[27] and one uncontrolled study[24]) or chronic heart failure NYHA class II–III (in one randomised clinical trial[22] and one uncontrolled study[25]). In one study[23] the effect of WS 1442 was investigated against digitoxin in healthy volunteers. In the ten randomised clinical trials, 733 patients were examined: 395 were treated with WS 1442 and 338 with placebo or control.

In three randomised clinical trials,[16,19,20] assessing 68 patients in the WS 1442 group and 68 in the placebo or control group, no adverse events were observed in the hawthorn, placebo or control groups. In two randomised clinical trials,[17,23] assessing 39 patients in the WS 1442 groups and 39 in the placebo or control groups, there was no mention of adverse events. In the remaining five randomised clinical trials,[14,15,18,21,22] assessing 288 patients treated with WS 1442 and 231 patients with placebo or control, 30 patients who received hawthorn and 34 patients who received placebo or control reported adverse events. The most frequent were back pain, dizziness/vertigo and flu-like symptoms in the WS 1442 groups and dizziness/vertigo and headache in the placebo and control groups.

The manifestation of adverse events in the WS 1442 groups seems not to be linked to the dose used in the trials, as demonstrated by the study by Tauchert,[22] which used high doses. In the WS 1442 groups, 69 patients received 1800 mg/day, 70 patients received 900 mg/day and 70 patients received placebo. Twelve patients withdrew from the study and in two cases the withdrawal was a result of adverse events following hawthorn treatment (circulatory disturbance, chest pain and constipation). The incidence of adverse events was 26.1%, 28.6% and 51.4% in the groups treated with 1800 mg/day, 900 mg/day and placebo, respectively, and was therefore lower in patients treated with WS 1442 than in patients who received placebo. The most frequently adverse events reported were bronchitis, dizziness, vertigo, back pain, headache and flu-like symptoms. None of the adverse events were considered serious.

The fact that patients treated with hawthorn complained of fewer symptoms than patients who re-

**Table I.** Adverse events (AEs) reported in clinical trials on the use of hawthorn

| Study (year) | Indication | No. of patients (hawthorn/ placebo) | Dosage (mg/day) | Duration of treatment (wk) | Concomitant medication | AEs (n) | Authors' evaluation |
|---|---|---|---|---|---|---|---|
| **Herbal preparation: WS 1442** | | | | | | | |
| *Randomised clinical trials* | | | | | | | |
| Iwamoto et al. (1981)[14] | NYHA I–II | 35/45 | 180–270 | 6 | Not specified (glycosides dilatators and antiarrhythmic, antihypertensive and diuretic medications were not allowed) | Hawthorn: nausea (1)<br>Placebo: no AEs | "Despite continued intake of the medication the symptoms disappeared over a period of 6 weeks" |
| O'Connolly et al. (1987)[15] | NYHA I–II | 31/31 | 180 | 6 | Lipid-lowering drugs, cough and blood pressure medication, antidiabetics, diuretics, antirheumatics, enzymes | Hawthorn: dizziness (3)<br>Placebo: dry mouth (1); dizziness (1); visual disturbances (1); headache (1) | "A clear association between these adverse events and the medication could not be established" |
| O'Connolly et al. (1986)[16] | NYHA I–II | 33/33 | 180 | 6 | Not specified (psychoactive medication and circulatory active medication were not allowed) | Hawthorn: no AEs<br>Placebo: no AEs | "Adverse events were not observed during the treatment phase" |
| Hanak and Brûckel (1983)[17] | NYHA I–II | 29/29 | 180 | 3 | Not specified (circulatory active medication was not allowed) | Not reported | Not reported |
| Weikl et al. (1996)[18] | NYHA II | 63/66 | 160 | 8 | Calcium channel antagonists, ACE inhibitors | Hawthorn: dyspnoea, restlessness (1); stomach complaints (1); tachycardia, dizziness (1)<br>Placebo: dizziness (1); decrease of concentration (1); anxiety (1); stomach pain (1); pain (1) | "The tolerability of the active substance proved to be very good" |
| Eichstâdt et al. (2001)[19] | NYHA II | 20/20 | 480 | 4 | Aspirin (acetylsalicylic acid), nitrate, calcium channel antagonists, antidiabetics, lipid-lowering drugs, ACE inhibitors | Hawthorn: no AEs<br>Placebo: no AEs | "The tolerability of WS 1442 was very good" |
| Leuchtgens (1993)[20] | NYHA II | 15/15 | 160 | 8 | Not specified | Hawthorn: no AEs<br>Placebo: no AEs | "No adverse reaction occurred" |

*Continued next page*

**Table I.** Contd

| Study (year) | Indication | No. of patients (hawthorn/ placebo) | Dosage (mg/day) | Duration of treatment (wk) | Concomitant medication | AEs (n) | Authors' evaluation |
|---|---|---|---|---|---|---|---|
| Zapfe (2001)[21] | NYHA II | 20/19 | 240 | 12 | Not specified (cardiac glycosides, diuretics, calcium channel antagonists, ACE inhibitors and other hawthorn preparations were not allowed) | Hawthorn: no AEs<br>Placebo: allergic reaction (1) | "The study drug proved to be very tolerated, as adverse events did not occur" |
| Tauchert (2002)[22] | NYHA III | 69 (1800mg), 70 (900mg)/70 | 900–1800 | 16 | Triamterene hydrochlorothiazide | Hawthorn (900 mg/day): dizziness/ vertigo (3); back pain (4); flu-like syndrome (2); headache (2); arthritis (1); flatulence (1); gastroenteritis (1)<br>Hawthorn (1800 mg/day): dizziness/vertigo (1); bronchitis (4); back pain (1); flu-like syndrome (2); gastroenteritis (1)<br>Placebo: dizziness/vertigo (7); bronchitis (6); back pain (3); flu-like syndrome (2); headache (2); arthritis (1); flatulence (1); gastroenteritis (1) | "The tolerability was rated best for the 1800mg of WS 1442 group…WS 1442 appears to prevent dizziness, a condition which is frequently reported as an adverse event" |
| Staiger et al. (1987)[23] | Healthy volunteers | 10/10 (digitoxin as control) | 15 | Once | Not reported | Not reported | Not reported |
| *Uncontrolled studies* | | | | | | | |
| Eichstâdt et al. (1989)[24] | NYHA II | 20 | 480 | 4 | Not specified | Hawthorn: no AEs<br>Placebo: no AEs | "No drug related adverse events were observed" |
| Weikl and Noh (1992)[25] | NYHA II–III | 7 | 240 | 4 | Calcium channel antagonists, β-adrenoceptor antagonists (β-blockers), ACE inhibitors, cardioactive glycosides | Hawthorn: no AEs<br>Placebo: no AEs | "No adverse events were observed during the trial" |
| *Observational study* | | | | | | | |

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**Table I.** Contd

| Study (year) | Indication | No. of patients (hawthorn/ placebo) | Dosage (mg/day) | Duration of treatment (wk) | Concomitant medication | AEs (n) | Authors' evaluation |
|---|---|---|---|---|---|---|---|
| Tauchert et al. (1999)[26] | NYHA II | 1011 | 900 | 24 | Nitrates, calcium channel antagonists, ACE inhibitors, diuretics, β-blockers, cardioactive glycosides | 14 AEs were observed but only in two cases (abdominal discomfort and facial pain) was a possible relation with hawthorn postulated | "98.7% of the physicians noted a very good tolerance" |
| *Cohort study* | | | | | | | |
| Habs (2004)[27] | NYHA II | 130 | Not reported | 104 | Diuretics, ACE inhibitors, cardioactive glycosides, β-blockers | Not reported | Not reported |
| **Herbal preparation: LI 132** | | | | | | | |
| *Randomised clinical trials* | | | | | | | |
| Alexander (1995)[28] | NYHA II | 36/37 | 900 | 4–8 | Diuretics | Hawthorn: nervousness (1); heart pain (2); sleeplessness (2); hand tremor (1); nausea (1); cardiac complaints (1)<br>Placebo: nervousness (1) | "None of these adverse events required a reduction in dose" |
| Bôdigheimer and Chasa (1994)[29] | NYHA II | 36/37 | 300 | 4 | Diuretics | Hawthorn: migraine, nausea, flatulence (1); palpitations (1)<br>Placebo: stomach ache (1); nausea (1) | "Most of the adverse events were of unspecific nature" |
| Schmidt et al. (1994)[30] | NYHA II | 34/34 | 600 | 8 | Diuretics | Hawthorn: temporary nausea (1); cardiac complaints (1)<br>Placebo: dryness of the mouth (1); internal restlessness (1) | "The compatibility of preparation was good…it was doubted that the troubles reported were connected to test medication" |
| Tauchert et al. (1994)[31] | NYHA II | 65/59 (captopril as control) | 900 | 8 | Not specified (circulatory active medication was not allowed with the exception of diuretics) | Hawthorn: gastrointestinal complaints (2); heartaches (1)<br>Captopril: vertigo (1); headache (1); anxiety (1) | "No serious adverse events were reported under treatment" |
| Fischer et al. (1994)[32] | Effect on microcirculation | 12/12 | 900 | Once | Oral contraceptives | Hawthorn: no AEs<br>Placebo: no AEs | "Adverse events were not observed in any phase of the trial" |

*Continued next page*

**Table I.** Contd

| Study (year) | Indication | No. of patients (hawthorn/ placebo) | Dosage (mg/day) | Duration of treatment (wk) | Concomitant medication | AEs (n) | Authors' evaluation |
|---|---|---|---|---|---|---|---|
| Fôrster et al. (1994)[33] | NYHA II | 35/34 | 900 | 8 | Diuretics | Hawthorn: no AEs<br>Placebo: no AEs | "Significant adverse events were not observed, neither in the treatment group nor in the placebo group" |
| *Observational study* | | | | | | | |
| Schmidt et al. (1998)[34] | NYHA I–II | 3664 | 900 | 4–8 | Antidiabetics, analgesics, antirheumatics, lipid-lowering drugs, bronchodilatators | 48 patients reported 72 AEs: flush (3), palpitation (10); gastrointestinal complaints (24); pain in the heart (2); vertigo (7); itch (2); asthma (1), dyspnoea (4); weakness (2); chest pain (3); migraine, headache (7); epistaxis (2); anxiety (1); insomnia (1), somnolence (2); emesis (1) | "The high dosed crataegus extract proved to be well tolerated by the patients" |
| **Other herbal preparations** | | | | | | | |
| Rietbrock et al. (2001)[35] | NYHA II | 44/44 | 75 drops daily 3 mg/1mL (Rob 10) | 12 | Not specified | Hawthorn: 22 AEs were reported: one case of nausea was considered as probably associated with Rob 10. All other AEs were judged as not associated with Rob 10<br>Placebo: 26 AEs and one serious AE (eczema) were reported | "The present study proves the safety of crataegus extract"<br>"In one case of nausea the treating doctor suspected a causal association" |
| Degenring et al. (2003)[36] | NYHA II | 69/74 | 90 drops (Crataegisan®) | 8 | None | Hawthorn: 9 AEs<br>Placebo: 11 AEs (mild to moderate gastrointestinal, musculoskeletal, respiratory, urinary, vascular and psychiatric disorders) | "All were assessed by the treating physician as being unlikely related to the study medication" |
| Walker et al. (2002)[37] | Mild essential hypertension | 19/10 | 500 (hawthorn extract) | 10 | Not specified | Not reported | Not reported |

**NYHA** = New York Heart Association classification of chronic heart failure.

ceived placebo seems to indicate that this issue should be considered from an efficacy rather than a safety point of view: hawthorn appears to prevent rather than elicit dizziness, a condition that is frequently reported as an adverse event.

In the observational study, 1011 patients were treated with WS 1442 and monitored for 24 weeks.[26] The tolerance to treatment was considered by the physician to be good or very good: 14 adverse events occurred, but only two of these (abdominal complaints and facial pain accompanied by tachycardia) were described as having a 'possible' relationship with the hawthorn treatment.

In the two uncontrolled studies[24,25] no adverse events were observed during the trials, while in the cohort study[27] there was no mention of adverse events.

### 2.2 Clinical Studies with Crataegus Extract LI 132

Seven studies using LI 132 were identified; six randomised clinical trials[28-33] and one observational study[34] (table I). In five of the randomised trials,[28-31,33] hawthorn extract was used to treat chronic heart failure NHYA class II, while in the remaining randomised trial[32] the effect of hawthorn extract on the microcirculation was studied. In the observational study,[34] hawthorn was tested in patients experiencing heart failure NYHA I–II.

In the six randomised trials, 431 patients were studied; of these, 218 were treated with LI 132 and 213 were treated with placebo or control. In two studies,[32,33] no adverse events were reported in either the LI 132 or placebo group. In the other four studies,[28-31] assessing 171 patients treated with LI 132 and 167 with placebo, 15 adverse events were reported in the LI 132 group and 5 in the placebo group. The most frequent adverse event in the LI 132 group was nausea. Other adverse events were generally considered mild or moderate by the treating physicians: in just one case a patient reported migraine, nausea and flatulence described as considerable and evaluated by the physician as possibly linked to LI 132.[29]

In the observational study,[34] 3664 patients were monitored by 940 medical practitioners to evaluate the efficacy and the tolerability of high-dose LI 132 (900 mg/day). During this study, 72 adverse events were reported in 48 patients; in eight cases these events were considered severe (palpitations, n = 1; gastrointestinal complaints, n = 3; vertigo, n = 2; chest pain, n = 1; migraine, n = 1), whereas in the other cases the adverse events were classified as mild or moderate. Furthermore, the adverse events could be linked to hawthorn treatment in only 27 of 48 cases; in 22 of these cases the association was considered possible, whereas for the remaining five cases (palpitations, n = 2; gastrointestinal complaints, n = 1; vertigo, n = 1; chest pain, n = 1) the events were deemed to be definitely related to hawthorn intake.

### 2.3 Clinical Studies with Other Crataegus Extracts

In a placebo-controlled study investigating an extract of hawthorn berries (Rob 10; Robugen GmbII, Esslingen-Zell, Germany) 48 adverse events (22 in the hawthorn group and 26 in the placebo group) were reported.[35] Of these adverse events, only one was reported as serious (acute eczema). However, acute eczema also occurred in the placebo group. Most adverse events in the Rob 10 group were judged to be not associated with the study drug; only one case of nausea was considered as probably related to Rob 10. The other types of adverse events that occurred were not specified by the author.

In a study on patients with congestive heart failure NYHA class II by Degenring et al.,[36] 69 patients were treated with an extract of crataegus berries (Crataegisan®)[1] and 74 patients were treated with placebo. The patients received 30 drops of the extract three times daily, corresponding to a daily dose of at least 6.4mg of oligomeric procyanidines or at least 12.7mg of total phenolic compound. Nine

**1** The use of trade names is for product identification purposes only and does not imply endorsement.

patients in the hawthorn group and 11 patients in the placebo group reported adverse events, which were mild to moderate in severity. The association of the adverse events with the study medication was considered unlikely. The tolerability of the treatment was assessed as 'good' by 98.6% of the patients.

In the study by Walker et al.,[37] 500mg of hawthorn extract was tested in 19 patients with mild hypertension; there was no mention of adverse events.

## 3. Data from Spontaneous Reporting Schemes

No adverse event case reports were found in any of the databases searched with the exception of the WHO. As of January 2005, the WHO Collaborating Centre for International Drug Monitoring had received 18 case reports of adverse reactions involving hawthorn as the suspected drug. Most of these reports came from Germany (n = 10); the others come from France (n = 2), The Netherlands (n = 2), Switzerland (n = 1), the UK (n = 1), Canada (n = 1) and the US (n = 1).

All collected reports except one were spontaneous reports. In 11 cases the patients were female, in four they were male and in three the sex was not specified. In 41% of the cases the patients were aged >50 years; in one case the patient was 9 years old. In 16 reports, the suspected drugs were oral preparations containing extract from *C. laevigata*, taken as capsules or drops. In two cases the hawthorn extract was administered intravenously. In 11 cases hawthorn was administered as a monotreatment, whereas in four it was taken with other concomitant drugs; in the other three cases information on concomitant drugs was not available. The most frequent indication for the use of hawthorn extract was cardiovascular conditions; however, in eight cases the indication was not specified.

In most of the cases, the patient showed more than one symptom; 42 adverse events were reported in total (table II). The most frequent adverse events were dizziness (n = 6), nausea (n = 5), fall (n = 2), gastrointestinal haemorrhage (n = 2), circulatory failure (n = 2) and erythematous rash (n = 2). A case of meningomyelocele, brain damage and hydrocephalus was reported in a 28-year-old woman who took hawthorn extract and opipramol. A causal association between the adverse events and the use of both drugs was considered possible.

**Table II.** Adverse events reported in the WHO database

| Adverse event | n |
|---|---|
| **General symptoms** | |
| Excessive perspiration | 1 |
| Increased appetite | 1 |
| Loss of taste | 1 |
| Tremor | 1 |
| Rigors | 1 |
| Muscle stiffness | 1 |
| **Neurological symptoms** | |
| Dizziness | 6 |
| Fall | 2 |
| **Endocrinological signs** | |
| Hypothyroidism | 1 |
| **Gastrointestinal symptoms** | |
| Gastrointestinal haemorrhage | 2 |
| Abdominal pain | 1 |
| Diarrhoea | 1 |
| Nausea | 5 |
| **Cardiovascular symptoms** | |
| Bradycardia | 1 |
| Circulatory failure | 2 |
| Hypotension | 1 |
| Fibrillation cardiac | 1 |
| Sinus arrest | 1 |
| Ventricular extrasystole | 1 |
| **Psychiatric symptoms** | |
| Emotionality | 1 |
| Agitation | 1 |
| Somnolence | 1 |
| **Gynaecological symptoms** | |
| Menstrual disorders | 1 |
| Respiratory symptoms | 1 |
| Epistaxis | 1 |
| **Dermatological symptoms** | |
| Erythematous rash | 2 |
| **Other** | |
| Hydrocephalus | 1 |
| Brain damage congenital | 1 |
| Meningomyelocele | 1 |
| **Total** | **42** |

Most of the case reports do not include essential data for assessing the likelihood of a causal association; in fact, the dose of the drug, the duration of the treatment, the use of concomitant drugs and information regarding the patient were not always specified in the case reports received by the WHO. Also, the causality of association between the adverse events and the suspected drug was not specified in ten cases and not assessed in one case. In the remaining seven cases, the causality was assessed as possible; in four of these cases hawthorn was the only suspected drug, but in the other three hawthorn was taken with concomitant drugs. A dechallenge was specified in four cases; in the other 14 cases no such data were provided. In three of the four dechallenge cases, the drug was withdrawn and the adverse reaction subsequently abated; in one case the outcome of the withdrawal was unknown. A rechallenge was performed in only one case, after which the adverse reactions, vertigo and somnolence, recurred. However, this patient took five different herbal extracts at the same time (crataegus, passiflora, belladona, valerian, frangula) and all of them were suspected as being involved in the adverse events. When the intake of these extracts was stopped, the adverse events abated. The recurrence of vertigo and somnolence following the rechallenge in this patient was reported after the administration of all five extracts.

## 4. Data from Hawthorn Manufacturers

Of the eight manufacturers of hawthorn preparations who were contacted, three replied. Of the three that replied, two manufacturers did not give any information on safety data, while one manufacturer provided a general statement about a small number of non-serious adverse reactions reported in association with their hawthorn monopreparation. There was no further information.

## 5. Discussion

The use of preparations containing hawthorn leaves with flowers is considerable, especially in Germany. Many studies have been performed in order to evaluate the effectiveness of these preparations in patients with chronic heart failure. The evidence presented in this article suggests that hawthorn is not associated with frequent or serious adverse effects. However, the available information on safety is rather limited. This is a recurring phenomenon in herbal medicine, and often no rigorous attention is given to adverse events or interactions with synthetic drugs. This may be partly a result of the erroneous belief that herbal products are natural and therefore safe. Moreover, there is also evidence to suggest that patients are less likely to inform their physicians about adverse events from herbal drugs than from conventional medicines.[38]

Data from the 24 clinical studies identified in this systematic review involving 5577 analysed patients suggest that hawthorn preparations are well tolerated. In fact, 166 AEs were found in total. Nearly all of the identified studies were conducted using two different hawthorn extracts containing leaves and flowers: WS 1442 standardised to 18.75% oligomeric procyanidins and LI 132 standardised to 2.25% flavonoids. It seems that significant differences regarding the safety of WS 1442 and LI 132 do not exist. The frequency and the kind of adverse events reported in the WS 1442 and LI 132 trials appear to be similar. For both extracts, dizziness/vertigo, gastrointestinal complaints and headache/migraine are the adverse events most frequently reported. Moreover, most of the adverse events that occurred in the WS 1442 and LI 132 groups were also described in the placebo and control groups.

None of the AEs that could definitely be related to the use of hawthorn were considered serious and their incidence did not seem to be correlated with dosage. In fact, in the study by Tauchert,[22] the occurrence of adverse events was lower for the WS 1442 1800 mg/day group than for the WS 1442 900 mg/day group.

The most frequent adverse events were dizziness/vertigo (n = 15), gastrointestinal complaints (n = 24), headache (n = 9), migraine (n = 8) and palpitation (n = 11). In four studies, no mention of adverse events was made by the authors. Because both chronic heart failure and concomitant medications can cause symptoms that might be mistaken for

adverse effects of hawthorn, placebo-controlled randomised clinical trials generate more reliable safety data than other types of studies.

The spontaneous reporting schemes of the WHO reported 18 case reports following hawthorn treatment. A total of 42 adverse events were described, and the most frequent were dizziness, nausea, gastrointestinal haemorrhage, circulatory failure, erythematous rash and fall. One case of meningomyelocele, brain damage and hydrocephalus was reported in a 28-year-old woman who took a hawthorn extract and opipramol for depression disorders. In this case, as in other reports, the quality and quantity of the information are not sufficient to prove an association between hawthorn treatment and any specific adverse event; in fact, data on patient history, dose and treatment duration are usually not provided, and often the patients have taken concomitant drugs.

The information provided by manufacturers of hawthorn products was poor: only three replied and none of these provided additional safety data.

No drug interaction or contraindication emerged from the clinical studies or spontaneous reporting schemes. Data from reviews describing hawthorn properties suggest that hawthorn can be considered a safe and well tolerated herbal drug. The adverse events in these reviews were reported as mild or not relevant: headache, sweating, fatigue, dizziness, palpitation, mild rash, sleepiness, agitation and gastrointestinal symptoms.[1,10,39] However, in these reviews additional information about interactions and contraindications were supplied. For instance, if hawthorn is used with vasodilating drugs such as theophylline, caffeine, papaverine, sodium nitrate and adenosine, an increase in coronary artery dilation may occur. Some reviews[1,5,7] also report that hawthorn could potentiate the action of digitalis glycosides and therefore a possible reduction in the digoxin dose may be required, but further studies are needed regarding this issue, because another study reported an interaction between hawthorn and digoxin.[40]

Hawthorn use should be avoided in women during pregnancy as well as during lactation, even if no increase in the frequency of malformation or other harmful effects on the fetus has been reported.[41] In addition, hawthorn should also be avoided in patients who are allergic to plants from the *Rosaceae* family.

## 6. Conclusion

In conclusion, although further studies are needed to assess the safety of hawthorn-containing preparations, all data reviewed here indicate that hawthorn is rarely associated with serious adverse events. However, the unsupervised use of this drug can be associated with problems, especially if given with concomitant medications.

## Acknowledgements

The authors wish to thank Dr Antonella Di Sotto, Department of Pharmacology of Natural Substance and General Physiology, University of Rome, 'La Sapienza', Rome, Italy, for her support.

No sources of funding were used to assist in the preparation of this review. The authors have no conflicts of interest that are directly relevant to the content of this review.

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