Hawthorn (Crataegus spp.) in the treatment of cardiovascular disease

Mary C. Tassell, Rosari Kingston¹, Deirdre Gilroy², Mary Lehane³ and Ambrose Furey

Team Elucidate, Department of Chemistry, Cork Institute of Technology (CIT), Bishopstown, Cork, Co. Cork, ¹West Cork Herb Farm, Knockeens, Churchcross, Co. Cork, and ²Department of Biological Sciences, CIT, ³Department of Applied Sciences, Limerick Institute of Technology, Moylish Park, Limerick, Ireland.

Submitted: 10-03-2010 Revised: 22-04-10 Published: 10-07-10

ABSTRACT

The medicinal properties of hawthorn (Crataegus spp., a genus comprising approximately 300 species) have been utilized by many cultures for a variety of therapeutic purposes for many centuries. In the Western world cardiovascular disease (CVD) has become one of the single most significant causes of premature death. Echoing this situation, more recent research into the therapeutic benefits of hawthorn preparations has focused primarily upon its cardiovascular effects. This review covers research into the various mechanisms of action proposed for Crataegus preparations, clinical trials involving Crataegus preparations, and the herb’s safety profile.

Clinical trials reviewed have been inconsistent in terms of criteria used (sample size, preparation, dosage, etc) but have been largely consistent with regard to positive outcomes. An investigation into data available to date regarding hawthorn preparations and herb/drug interactions reveals that theoretical adverse interactions have not been experienced in practice. Further, adverse reactions relating to the use of hawthorn preparations are infrequent and mild, even at higher dosage ranges. A recent retrospective study by Zick et al. has suggested a negative outcome for the long-term use of hawthorn in the prognosis of heart failure. These findings are examined in this paper.

Although further research is needed in certain areas, current research to date suggests that hawthorn may potentially represent a safe, effective, nontoxic agent in the treatment of CVD and ischemic heart disease (IHD).

Key words: Cardiovascular disease, Crataegus, hawthorn, whitethorn

INTRODUCTION

This paper aims to provide a comprehensive overview of research into the effectiveness of Crataegus preparations in the treatment of cardiovascular disease (CVD) to date. The paper includes information concerning the recent research regarding the identification of perceived active constituents and their mechanisms of action. Current research involving clinical trials utilizing Crataegus preparations is also reviewed. Other areas explored include drug–herb interactions and the safety profile of this remedy.

The World Health Organisation (WHO) lists cardiovascular disease (CVD) as globally the number one cause of death, accounting for 30% of all deaths in 2005.[5] The American Heart Association cites heart disease as the number one killer of American adults,[6] and further commented that for the year 2005, 80,700,000 Americans suffered from some form of CVD.

The use of nonvitamin/nonmineral supplements among the elderly population is increasing.[7] Crataegus supplements have been listed as one of the remedies popular with this age group. There is approximately a one-in-three incidence of complementary and alternative medicine over-the-counter use in patients suffering chronic heart failure (CHF). An increased over-the-counter use of Crataegus preparations, coupled with a high incidence of patients failing to report use of these preparations with concomitant orthodox medications, indicates a need to ensure that Crataegus preparations do not present with any potential complications regarding herb/drug interactions.[8]

The medicinal use of hawthorn in CVD is prevalent in most cultures. Direct comparisons between the phytochemical profiles of these species used worldwide have not been undertaken, although indigenous use would indicate a high degree of confluence.

CONSTITUENTS AND THEIR MECHANISMS OF ACTION

The Irish physician who was first noted to have used the remedy...
for cardiovascular complaints specifically used berries. The 1983 edition of the British Herbal Pharmacopoeia, regarded by many as the standard text for professional herbalists for many years, cites berries only. This may explain practicing herbalists noted the 1983 edition of the British Herbal Pharmacopoeia, regarded by many practitioners, noted the 1983 edition of the British Herbal Pharmacopoeia, regarded by many practitioners, noted for cardiovascular complaints specifically used berries. The 1983 edition of the British Herbal Pharmacopoeia, regarded by many as the standard text for professional herbalists for many years, cites berries only. This may explain practicing herbalists noted preference for berry over flower, although this trend seems to be changing in recent times, flowers and berries being utilized more interchangeably, and in some cases blended. Historical texts in Western medicine record the use of berries, seeds, and flowers. Leaves are also used.

The identification of constituent groups such as bioflavonoids and proanthocyanidins has shed light on some of the beneficial effects of *Crataegus* on the cardiovascular system. Bioflavonoids now being well established as possessing significant antioxidant activity. Berries, leaves, and flowers of hawthorn are phytochemically similar in composition, differing primarily in the ratio of specific flavonoids and proanthocyanidins present. Berries are rich in hyperoside, while leaves contain higher levels of vitexin-2-rhamnoside. Kingston detected significant levels of vitexin-2-rhamnoside in flowers. Mills states that the flowers contain higher levels of flavonoids, the leaves containing the highest levels of oligomeric procyanidins (OPCs). Higher levels of proanthocyanidins present in leaves was established by Vanhaelen et al. To date a number of different potential actions have been suggested, many of which are theoretical as human studies remain small in number.

Table 1 details research concerning the mechanisms of action of *Crataegus*. In many studies, whole plant extracts or OPC/flavonoid combinations were utilized rather than specific isolated classes of phytochemicals. This approach, while more realistic in terms of the actions of the whole plant, makes it difficult to attribute mechanisms of action demonstrated to specific active constituents in every case. Also, antioxidant activities appear to be common to both the OPCs and the flavonoid group, conferring a considerable generalized benefit from both of these constituent groups in chronic illness.

**Table 1: Mechanisms of action of hawthorn – Areas of influence on the cardiovascular system**

<table>
<thead>
<tr>
<th>Antioxidant</th>
<th>Hypotensive</th>
<th>Antiatherosclerotic</th>
<th>Action on cardiac cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct scavenging of reactive oxygen species</td>
<td>Antioxidant activities</td>
<td>Antioxidant activities</td>
<td>Antioxidant activities</td>
</tr>
<tr>
<td>Enhanced superoxide dismutase and catalase activities</td>
<td>Vasorelaxation via stimulation of nitrous oxide synthase</td>
<td>Vasorelaxation effects on smooth muscle</td>
<td>Vasorelaxation activities</td>
</tr>
<tr>
<td>Protective function for alpha tocopherol</td>
<td>Vasorelaxant effects on smooth muscle</td>
<td>Weak ACE activity</td>
<td>Vasorelaxation activities</td>
</tr>
<tr>
<td>Increased cell viability and protection of gap junction intracellular communication</td>
<td>Downregulation of capsaicin-3 gene expression</td>
<td>Regulation of lipoprotein lipase expression</td>
<td>Downregulation of capsaicin-3 gene expression</td>
</tr>
<tr>
<td>Inhibition of tyrosinase and lipoxygenase activity, plus hydroxyl radical scavenging activity</td>
<td>Increased excretion of bile acids via upregulation of the activity of cholesterol 7 a hydroxylase</td>
<td>Reduced activity of intestinal Acyl CoA cholesterol acyltransferase, leading to the inhibition of absorption of dietary cholesterol</td>
<td>Inhibition of 3,5-cyclic adenosine monophosphate phosphodiesterase, resulting in increase in coronary flow, increase in relaxation velocity, slight positive inotropic effects, and slight raise in heart rate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronotrophic and antiarrhythmic actions</td>
</tr>
</tbody>
</table>

Epidemiological evidence indicates significant links between increased dietary flavonoid intake and reduction in coronary-related mortality. Negative chronotrophic effects and antiarrhythmic effects of crude hawthorn extracts on cultured cardiomyocytes were noted by Long et al., who further stated that hawthorn’s chronotrophic mechanism of action is unlikely to involve β-adrenergic receptor blockade. The study involved cardiomyocytes sourced from mice.

Of the 15 pieces of research considered in Table 1, only four involved the use of human volunteers or human tissue. These are of most relevance as they most closely replicate actual human in vivo environments. Vasorelaxant effects on vascular smooth muscles previously artificially contracted by catecholamines were noted by Vierling et al. who postulated that this could have significant clinical importance as raised catecholamine levels are present in the blood stream during heart failure. Endothelial-dependent nitrous oxide induction, triggering vasodilation, has been attributed primarily to oligomeric procyanidins. Vasorelaxant effects reduce peripheral vascular resistance and increase coronary blood flow. In chronic heart failure, sympathetic nervous system stimulation offers short-term benefits regarding circulatory support but is deleterious in the long term, inducing a hypertensive state. Vasorelaxation would therefore be beneficial.

The antioxidant activity of *Crataegus* preparations contributes significantly to its therapeutic profile. Gou et al. noted that of 28 fruit pulps tested, the hawthorn pulp (Chinese hawthorn) produced the highest measure of antioxidant activity. A similarly high antioxidant activity in *Crataegus aronia*, a hawthorn indigenous to Israel, Jordan, and the Palestine, has been found. The IC50 values of specific active constituents have been established in relation to the antioxidant capacity, with values of epicatechin and hyperoside being significantly lower (more effective) than those of established antioxidant drugs (i.e., glutathione and N-acetylcysteine). Oligomeric proanthocyanidins
appear to possess a higher antioxidant activity used in isolation than polymeric proanthocyanidins (PPCs) used in isolation. However, the removal of PPCs from a mixture may result in a less actively protective medicine, possibly partially due to their high concentration influencing outcome.

IC50 represents the amount of a substance/drug required to inhibit 50% of a given process.

Significant protective effects on cardiovascular cells were noted by Ling et al. using a whole plant extract of Chinese hawthorn (plant part not stated). It was postulated that this could be mediated by the regulation of the capaspe signal pathway, affecting the reduction of endothelial cell apoptosis. The study also highlighted the potential for the four herbs tested to reduce cells’ ability to regenerate and repair a negative finding. The exact nature of the herbal products under study was not given (no plant part stated, no preparation technique elucidated); therefore, this finding is difficult to interpret.

In studies not directly related to cardiovascular effects, immunomodulatory effects were not detected in Crataegus preparations, although the potential for suppression of interleukin 2 has been cited. Flavonoid and procyanidin compounds have demonstrated an antiviral activity in vitro.

Some protective effects in ischemia/reperfusion injury have been reported, primarily relating to ex vivo animal studies. No studies in this area on human tissue appear to have been conducted to date. The pharmacodynamic profile of hawthorn extracts has been examined in animal studies, but no studies appear to have been performed on human subjects.

CLINICAL TRIALS AND RELATED RESEARCH

Table 2 provides details of nine trials undertaken between 1990 and 2008. The findings reflect a meta-analysis undertaken by Pittler et al., who studied eight randomized, placebo-controlled trials. This study showed Crataegus extract to demonstrate definite benefits in the treatment of CHF over placebo. In common with the data examined by Pittler et al., the parameters utilized in the various study designs detailed below vary significantly.

A heterogeneous array of Crataegus-based medicines is represented in the clinical trials reviewed here, with WS1442 being the most common. Numbers of patients involved in the trials varied, those undertaken by Hellenbrecht et al. and Zapfe et al. being so low (18 and 40, respectively) as to question the significance of the results. The use of the cohort study technique by Habs may result in significant dissimilarities existing in the two study cohorts, as the physician’s criteria for determining who receives the Crataegus extract and who does not may introduce bias. Thus there is a danger that the study is not comparing like with like. The study’s strengths lie in the large number of participants, the extended time scale (>2 years), and the matched-case control technique employed to minimize dissimilarities between the two groups. Long-term results from this study do not appear to be available. Where consistency was present concerning the remedy used (i.e., WS1442), dosage administered to participants varied from 240 mg per day to 1800 mg per day. Four studies involved patients also taking concurrent orthodox cardiovascular medications, while four did not (one involved patients on orthodox diabetic medications). Three of the studies were of short duration, ranging from 8 to 12 weeks. Two of these studies investigated exercise tolerance/circulatory stress tolerance and found improvements within this timeframe. The third study (8 weeks) recorded improvements in all parameters except blood pressure. Furey and Tassell however note that the findings of Asgary et al. demonstrated that hypotensive effects were specifically detected after 3 months of treatment. Thus the 8 weeks of the trial might not have been the sufficient study length for the hypotensive effects to become apparent.

The study by Holubarsch et al. failed to establish significant differences in rates of cardiac death, nonfatal myocardial infarction, and hospitalization between the two treatment groups, but highlighted potential benefits for the remedy in the treatment of patients with heart failure at risk of sudden cardiac death. The ambivalent findings recorded by Holubarsch et al. regarding the primary endpoint may be in part due to insufficient dosage levels being utilized among this patient group, a significant number of whom have NYHA III heart failure. Tauchert’s findings of dose-dependent improvements in clinical signs and symptoms, coupled with improved exercise tolerance among patients with NYHA III heart failure, would indicate higher dosage levels as desirable. Specifically, this study noted significant improvements at the higher dosage level of 1800 mg per day, as opposed to the data used by Zick et al. and Holubarsch et al., who used 900 mg per day. Future trials to determine the optimal therapeutic dosage for this patient group have been suggested.

Although the study by Holubarsch did not detect the clinical improvements sought, neither did it detect significant adverse findings, and many of the parameters measured yielded positive, although not statistically significant, results. Significantly fewer patients in the Crataegus cohort were noted by Habs et al. to require orthodox medications such as ACE inhibitors and cardiac glycosides than in the comparative cohort. Diuretics and beta blockers were also less frequently prescribed. This finding was also noted by Zick et al. with regard to reduced need for diuretic medications in the Crataegus cohort.

The varied nature of parameters used in the above trials, although potentially confusing, is of interest as the outcomes are largely the same. No matter what parameters change the outcome is positive. This is significant in its own way, although the concept of publication bias in clinical research should also be acknowledged. The only obvious exception to this finding is the change in the patient profile in terms of the increased severity of illness (NYHA stage III and above) which may require higher dosage levels to elicit therapeutic benefit. The Expanded Commission
### Table 2: Clinical trials and related studies conducted to date

<table>
<thead>
<tr>
<th>Author(s) and date</th>
<th>Nature of the trial</th>
<th>Hawthorn preparation</th>
<th>Dosage</th>
<th>No. of patients</th>
<th>Trial length</th>
<th>Pathology</th>
<th>Current medication</th>
<th>Measurements</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holusbarsch et al. 2008 SPICE trial[^6]</td>
<td>Randomized, double-blind, placebo-controlled, multicentre study</td>
<td>WS1442</td>
<td>900 mg per day</td>
<td>2681</td>
<td>24 months</td>
<td>NYHA stage II and III (LVEF &lt; 35%)</td>
<td>Beta blockers, ACE inhibitors, diuretics, digoxin/digitoxin</td>
<td>Time until first cardiac event</td>
<td>No effect on primary endpoint. May potentially reduce incidence of sudden death in patients with less compromised LVF.</td>
</tr>
<tr>
<td>Zick et al. 2008[^7]</td>
<td>Retrospective study on data obtained from the HERB CHF trial (6-month randomized, double-blind, placebo-controlled study)</td>
<td>WS1442</td>
<td>900 mg (450 mg twice daily)</td>
<td>120</td>
<td>6 months</td>
<td>Stage II–IV NYHA heart failure</td>
<td>ACE inhibitors, ARB, spironolactone, beta-blockers, loop diuretics, thiazide, diuretics, digoxin</td>
<td>Primary goal to measure long term effects of Crataegus preparations</td>
<td>Nominally more heart failure deaths in Crat group (3.3%; 2/60 vs 1.6%; 1/60)</td>
</tr>
<tr>
<td>Walker and Marakis 2005[^32]</td>
<td>Randomized, double-blind, placebo-controlled study</td>
<td>Hawthorn extract (Faros 600 [LI 132, Lichtwer Pharma, Berlin] extract 3:1, standardized to 2.2% flavonoids)</td>
<td>1200 mg bd equivalent to 6 g dried flower tops</td>
<td>80</td>
<td>16 weeks</td>
<td>Type 2 diabetes and hypertension</td>
<td>Diabetic medications, inc. low-dose insulin and hypoglycemic drugs, 71% = hypertensive drugs</td>
<td>Blood pressure</td>
<td>Modest reduction in diastolic BP in hawthorn group.</td>
</tr>
</tbody>
</table>

[^6]: Hawthorn and cardiovascular disease

[^7]: Hawthorn and cardiovascular disease
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Interventions</th>
<th>Duration</th>
<th>Primary Outcome Measure</th>
<th>Adverse Events</th>
<th>Blood Pressure Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asgary et al. 2004&lt;sup&gt;[44]&lt;/sup&gt;</td>
<td>Randomized, double-blind, placebo-controlled trial</td>
<td>Hydroalcoholic extract of Crataegus curvisepal, a flower. 1:8 tincture via percolation</td>
<td>20 drops three times daily</td>
<td>More than 4 months</td>
<td>Primary mild hypertension</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood pressure decrease in both systolic and diastolic blood pressure after third month (p=&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Habs&lt;sup&gt;[36]&lt;/sup&gt; 2004</td>
<td>Prospective cohort study</td>
<td>WS1442 One cohort on orthodox medication only, the other on Crataegus preparation as add on or monotherapy</td>
<td>Not stated</td>
<td>Heart failure, stage NYHA II</td>
<td>Standard orthodox medications, including ACE inhibitors, diuretics, beta blockers, and cardiac glycosides</td>
<td>Fatigue, Dyspnea, Palpitations, Nocturia, Edema, Heart rate, Blood pressure, Quality of life: Minnesota Living with Heart Failure Questionnaire, EuroQoL EQ5D</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All parameters in Crataegus group showed comparable or superior improvements to cohort comparison. The three cardinal symptoms of heart failure, fatigue, stress dyspnoea and palpitations = significantly reduced in Crataegus cohort compared to comparative cohort.</td>
</tr>
<tr>
<td>Degenring et al.&lt;sup&gt;[37]&lt;/sup&gt; 2003</td>
<td>Randomized, double-blind, parallel group, multicentre, placebo-controlled study</td>
<td>Standardized extract fresh Crataegus berries (Crataegisan)</td>
<td>3 × 30 drops (N = 69) or placebo (N = 74)</td>
<td>8 weeks</td>
<td>Cardiac failure (NYHA class II)</td>
<td>Concomitant medication excluded</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exercise tolerance (cycle), Blood pressure-heart rate product</td>
<td>Significant improvement in dyspnoea and fatigue.</td>
</tr>
<tr>
<td>Tauchert&lt;sup&gt;[16]&lt;/sup&gt; 2002</td>
<td>Randomized, double-blind, placebo-controlled, multicentre trial</td>
<td>WS1442 (dry extract of hawthorn leaves and flowers)</td>
<td>1800 mg or 900 mg or placebo</td>
<td>16 weeks</td>
<td>Chronic congestive heart failure (NYHA class III)</td>
<td>Previously untreated or treated with diuretics and/or low-dose ACE inhibitors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Exercise capacity (cycle), Subjective symptoms</td>
<td>Improved exercise capacity, Symptom reduction</td>
</tr>
<tr>
<td>Schroder et al.&lt;sup&gt;[38]&lt;/sup&gt; 2001</td>
<td>Multicentre, nonrandomized cohort study</td>
<td>Cranolin (homeopathic preparation)</td>
<td>Cranolin 20 drops tds (80%) or 10 drops tds (15%)</td>
<td>8 weeks</td>
<td>Mild cardiac insufficiency (NYHA class II)</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Various, including staircase test, walk test, nocturnal urination, dyspnea,</td>
<td>Crataegus based Cranolin was non-inferior to ACE inhibitor/diuretic treatment in all areas except BP reduction</td>
</tr>
</tbody>
</table>

Table 1 (contd...)
Table 1 (contd.)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zapfe (2001)</td>
<td>Randomized, placebo-controlled, double-blind study</td>
<td>WS1442 240 mg (80 mg tds)</td>
<td>12 weeks Mild chronic heart failure (NYHA class II)</td>
<td>Cardiovascular medications excluded</td>
</tr>
<tr>
<td>Hellenbrecht et al. (1990)</td>
<td>Randomized, placebo-controlled study</td>
<td>Extract of Crataegus (CRAT) (Kneipp Planzen-Dragées Weissdom) 3 tid (concentration = not stated)</td>
<td>4 weeks Healthy subjects, challenged with catecholamines</td>
<td>None stated</td>
</tr>
</tbody>
</table>

*A total of 952 patients were initially recruited for this study. This report details interim results on findings after the first 2 years.

The phenomenon of the increased likelihood of patients in the CRAT Special Extract WS1442 group in the recent study by Zick et al. (7) to experience a heart failure progression event at baseline (3.9 times more likely), and the subsequent decrease of this risk over time have no rational explanation and have not been observed by other studies, indicating anomalous findings.

Holubarsch et al. reported a statistically nonsignificant increase in hospitalization due to progression of heart failure, but this was countered by a significant decrease in the incidence of sudden cardiac death, and overall number of patients experiencing a cardiac event was lower (statistically nonsignificant) in the WS1442 cohort.

Zick et al. commented that their results may be due to chance as the sample size was small, rendering it more vulnerable to a significant impact from chance outcomes which would produce anomalies in the findings. Also, the sample group in this nature has not been studied, but the data, if available, would be critical.

The SPICE trial specifically looked at mortality and morbidity as endpoints. The study concluded that the primary endpoint, progression heart failure, was not achieved. The study did not reach statistical significance. It was suggested that WS1442 may reduce sudden cardiac deaths in patients with LVEF between 25% and 35%.

Belz et al., reported findings of dose-response-related efficacy of a camphor-Crataegus product (Korodin) in randomized, placebo-controlled studies. Delez et al. reported findings of dose-response-related efficacy of a camphor-Crataegus product (Korodin) in randomized, placebo-controlled studies. Delez et al. reported findings of dose-response-related efficacy of a camphor-Crataegus product (Korodin) in randomized, placebo-controlled studies. Delez et al. reported findings of dose-response-related efficacy of a camphor-Crataegus product (Korodin) in randomized, placebo-controlled studies. Delez et al. reported findings of dose-response-related efficacy of a camphor-Crataegus product (Korodin) in randomized, placebo-controlled studies. Delez et al. reported findings of dose-response-related efficacy of a camphor-Crataegus product (Korodin) in randomized, placebo-controlled studies.

The issue of dosage, as discussed above, may be of considerable significance here also, as the additional antagonist spironolactone used by some patients in the HRBC CHF trial displays potential for a range of serious side effects, including electrolyte imbalances and hypotension. The expected incidence of adverse HF events in this nature has not been discussed. These data, if available, would be critical.

The expected incidence of adverse HF events in this nature has not been discussed. These data, if available, would be critical.

The expected incidence of adverse HF events in this nature has not been discussed. These data, if available, would be critical.

The expected incidence of adverse HF events in this nature has not been discussed. These data, if available, would be critical.

The expected incidence of adverse HF events in this nature has not been discussed. These data, if available, would be critical.

The expected incidence of adverse HF events in this nature has not been discussed. These data, if available, would be critical.

The expected incidence of adverse HF events in this nature has not been discussed. These data, if available, would be critical.
rapid initial effect, whereas *Crataegus* berries add a longer lasting pressor effect.[68] This would confirm the findings of Asgary et al. concerning the 3-month time span for pressor effects of Crataegus to become measurable.[69]

Both the HERB CHF study and the SPICE trial involved patients who were significantly more ill than those in many of the previous studies. This may well have influenced the outcome. *Crataegus*-based remedies at the dosage utilized may be primarily suited to mild or moderate cases of heart failure only. The slightly higher number of NYHA stage III patients in the *Crataegus* group (N = 30, 50%) in the HERB CHF study compared to those in the placebo group (N = 27, 45%) might have a detrimental impact on the results where participant numbers are small.

Mechanisms of action of *Crataegus* postulated to date reveal a remedy with potentially broad-based influence on the cardiovascular system. These effects include a hypotensive activity[17,22] via vasorelaxation resulting from nitrous oxide stimulation, significant antioxidant activity,[40-61] and a tonic action on cardiac myocytes.[15,52]

**SAFETY PROFILE OF CRATAEGUS PREPARATIONS**

**Side effects**

*Crataegus* preparations have been consistently proven to be well tolerated by patients with low/negligible levels of side effects.[20,33,36,37,53-55] Daniele et al. looked at data from 24 clinical trials and a total of 5577 patients.[54] They concluded that hawthorn preparations are generally well tolerated and noted that adverse effects were significantly lower in treatment groups using WS1442. It was noted that *Crataegus* appears to prevent dizziness rather than causing it. Further examination of spontaneous reporting schemes highlighted 18 case reports following *Crataegus* treatment, but stated that in many cases insufficient data were supplied to prove any association between *Crataegus* and specific adverse effects.[56] There appears to be no substantial body of evidence to suggest that *Crataegus* causes anything other than infrequent, mild adverse effects. There are also no known contraindications to its use during pregnancy,[6] although expert advice should be sought in this circumstance. *Crataegus* demonstrates low toxicity, with an LD50 of 25 mg/kg[57] and a high therapeutic index.[58] The clinical trial conducted by Tauchert et al. utilized a high dose of WS1442 (1800 mg) with no reported side effects.[6] Animal studies on *Crataegus* toxicity, using doses of WS1442 up to 100 times normal dose, showed no evidence of toxicity. Studies on human models of this nature have not been undertaken. The inotropic properties of *Crataegus* may theoretically cause concern, as the use of inotropes in the treatment of heart failure has been strongly linked to increased mortality rates.[59] The one orthodox inotrope not associated with this phenomenon is digoxin, which demonstrates weak inotropic effects, coupled with therapeutic benefits via other mechanisms (i.e., neurohormonal).[59] In that, it is not simply an inotroph but possesses a broad spectrum of other actions; *Crataegus* shares its therapeutic profile with digoxin and is thus unlikely to present with long-term adverse effects. An increase in the mortality rate resulting from the positive inotrophic effect of *Crataegus* was not detected in most recent clinical trials.[60] Kernan et al. highlighted concern regarding toxic side effects associated with digitals medications. Specifically, they examined the potential for acute, coincident illness to engender digitals toxicity due to decreased drug clearance. This potential risk appears to be largely avoided in *Crataegus* treatments due to its wide therapeutic index, coupled with the minimal incidence of serious side effects.[61] The need for good quality clinical studies examining mortality as an endpoint has been highlighted.[55,58,62] This issue has been addressed by Holusharsh et al.[63] in a study lasting 24 months, which showed no significant statistical differences between placebo or treatment groups in terms of mortality.

**Drug/Herb interactions**

Many different theoretical interactions between *Crataegus* and orthodox medications have been postulated. None have been substantiated. An interaction study between digoxin and *Crataegus* preparation WS1442 concluded that both of these remedies may be co-administered safely.[63] Three randomized clinical trials and one observational study reviewed by Daniele et al. involved concomitant use of cardiovascular glycoside medications. None of these studies raised any issues regarding herb/drug interactions. Vasodilatory effects of hawthorn have been cited as theoretically causing complications when used with other vasodilatory agents (i.e., caffeine, theophylline).[54] No reports of adverse effects relating to this issue have been cited to date. Inotropic actions of hawthorn have been cited as potentially affecting the hypotensive effects of beta blockers.[64] This also remains unsubstantiated. The proposed theoretical herb/drug interaction between *Crataegus* preparations and orthodox medications remains theoretical, possibly due to the complex effects of whole plant medicines upon the system.

The impact of the phytochemical synergistic interactions occurring within whole plant remedies is vital to a more intelligent and rational understanding of the nature of their mechanisms of action. Pharmacodynamic and pharmacokinetic interactions have already been researched[65] in whole plant medicines and the concept that identified constituents, singly or in groups, do not act in isolation but exert their effects in a more interactive and synergistic manner has been increasingly postulated by researchers.[15,20,54,66] This issue may well have relevance in the question of drug–herb interactions, where the broad-based nature of whole plant remedies poses a significantly reduced risk. This whole area requires further research if optimal therapeutic benefits are to be derived.

**CONCLUSIONS**

Results recorded from clinical trials, experiences of professionally qualified medical herbalists, and the low/negligible incidence of
side effects experienced by patients would indicate that *Crataegus* preparations hold significant potential as a useful remedy in the treatment of CVD.

Clinical trials have until recently been largely confined to patients presenting with NYHA stage I or II heart failure. More recently, the inclusion of patients with more advanced CVD in clinical trials might have affected outcomes, particularly where dosages were not adjusted to reflect the severity of illness.

Studies by Holusbarsch et al.[33] would indicate efficacy of *Crataegus* preparations in the treatment of mild to moderate heart failure (NYHA I–II). The more seriously ill patient may need higher dosages (1800 mg) as used by Tauchert[36] for significant improvements to be obtained. Ultimately, an examination of the data to date is encouraging but would point to the need for a more targeted approach in terms of dosage related to severity of illness. It is possible that this remedy might have limited the benefit for more seriously ill patients, but, used in the early stages of disease progression, may significantly enhance prognosis.

The excellent safety profile of this remedy, coupled with the lack of herb–drug interactions detected to date in clinical trials would further support its inclusion in treatment strategies surrounding CVD, especially in the early stages of disease progression.

A robust and succinct response to a letter to the editor of the European Journal of Heart Failure, criticizing the inclusion of a clinical trial involving the use of a homeopathic *Crataegus* preparation in the treatment of heart failure[70] called for a more targeted approach in terms of dosage related to severity of illness. It is possible that this remedy might have limited the benefit for more seriously ill patients but, used in the early stages of disease progression, may significantly enhance prognosis.

ACKNOWLEDGMENTS

We gratefully acknowledge funding from Technology Sector Research: Strand 1; Post-Graduate RandD Skills Programme in Institutes of Technology – 2005 for M. C. Tassell and the Council of Directors, Technological Sector Research – Strand III 2006 Grant Scheme, awarded to Dr. A. Furey.

REFERENCES

12. Kingston R. A phytochemical analysis of selected constituents of *Crataegus* flos and fruct. to determine whether ethanol, whiskey and brandy solvents affect the chemical constituent profile of the herbal preparations 2007, Scottish School of Herbal Medicine.


34. Habs M. Prospective, comparative Cohort Studies and Their Contribution to the benefit Assessments of Therapeutic Options: Heart Failure Treatment with and without Hawthorn Special Extract WS 1442. Forsch Komplementarmed Klass Naturheilkd 2004;11:36-9.


Source of Support: Nil, Conflict of Interest: None declared

Subscription rates for the year 2010

<table>
<thead>
<tr>
<th></th>
<th>Print</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Individual</td>
</tr>
<tr>
<td>India (INR)</td>
<td>2000</td>
</tr>
<tr>
<td>Overseas (US$)</td>
<td>400</td>
</tr>
</tbody>
</table>

- Published Semi Annual (January, July)
- Subscriptions are for calendar year only
- Please return this coupon to:
  Medknow Publications and Media Pvt. Ltd.
  B-9, Kanara Business Centre, Off link road, Ghatkopar (E),
  Mumbai – 400075, INDIA
- Cheque should favour “Medknow Publications And Media Pvt. Ltd.”
- Please allow at least six to eight weeks for commencement of new subscription.
- Claims for missing issues can be made only within one month of publication
- Agent’s discount: 5% (Should include the form giving details of end user)