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

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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.[3] The American Heart Association cites heart disease as the number one killer of American adults,[8] and further commented that for the year 2005, 80,700,000 Americans suffered from some form of CVD.

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The use of nonvitamin/nonmineral supplements among the elderly population is increasing.[9] *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.[10]

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.[5] 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.[11] 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 procyanidins 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.[12] Mills states that the flowers contain higher levels of flavonoids, the leaves containing the highest levels of oligomeric procyanidins (OPCs).[6] Higher levels of procyanidins present in leaves was established by Vanhaelen *et al.*[13] 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.

Epidemiological evidence indicates significant links between increased dietary flavonoid intake and reduction in coronary-related mortality.[14] Negative chronotrophic effects and antiarrhythmic effects of crude hawthorn extracts on cultured cardiomyocytes were noted by Long *et al.*,[15] 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.[16-19] 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.[20] Endothelial-dependent nitrous oxide induction, triggering vasodilation, has been attributed primarily to oligomeric procyanidins.[17,21,22] 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.[21] 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.[23] A similarly high antioxidant activity in *Crataegus aronia*, a hawthorn indigenous to Israel, Jordan, and the Palestine, has been found.[24] The IC50 values of specific active constituents have been established in relation to the antioxidant capacity,[25] 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

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

Antioxidant	Hypotensive	Antiatherosclerotic	Action on cardiac cells
Direct scavenging of reactive oxygen species[23,49,51]	Antioxidant activities[23,24,49,51,71]	Antioxidant activities [23,24,49,51,71]	Antioxidant activities[23, 24, 49, 51, 71]
Enhanced superoxide dismutase and catalase activities[49]	Vasorelaxation via stimulation of nitrous oxide synthesis[17,21,22]	Downregulation of capsase-3 gene expression[16]	Downregulation of capsase-3 gene expression[16]
Protective function for alpha tocopherol[24]	Vasorelaxant effects on smooth muscle[20]	Regulation of lipoprotein lipase expression[72]	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[52]
Increased cell viability and protection of gap junction intracellular communication[49]	Weak ACE activity[50]	Raised excretion of bile acids via upregulation of the activity of cholesterol 7 ά hydroxylase[19]	Chronotrophic and antiarrhythmic actions[15]
Inhibition of tyrosinase and lipoxygenase activity, plus hydroxyl radical scavenging activity[50]		Reduced activity of intestinal Acyl CoA cholesterol acyltransferase, leading to the inhibition of absorption of dietary chol[19]	
		Inhibition of thromboxane A2 (TXA2)	

appear to possess a higher antioxidant activity used in isolation than polymeric proanthocyanidins (PPCs) used in isolation.[18] 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.[18]

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).[16] It was postulated that this could be mediated by the regulation of the capsase 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.[26] Flavonoid and procyanidin compounds have demonstrated an antiviral activity *in vitro*.[27]

Some protective effects in ischemia/reperfusion injury have been reported,[28] 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,[29,30] 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[31] 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.*[32] and Zapfe *et al.*[33] 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-pairs 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,[7,34-36] 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.[32,37,38] 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.[38] Furey and Tassell[39] however note that the findings of Asgary *et al.* demonstrated that hypotensive effects were specifically detected after 3 months of treatment.[40] 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 Holusbarsch *et al.*[35] 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.[39] 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.*[7] and Holubarsch *et al.*[41] 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 Holubarsh 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.[34] Diuretics and beta blockers were also less frequently prescribed. This finding was also noted by Zick *et al.*[7] 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.[42] 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

Author(s) and date	Nature of the trial	Hawthorn preparation	Dosage	No. of patients	Trial length	Pathology	Current medication	Measurements	Results
Holusbarsch *et al.* 2008 SPICE trial[35]	Randomized, double-blind, placebo-controlled, multicentre study	WS1442	900 mg per day	2681	24 months	NYHA stage II and III (LVEF < 35%)	Beta blockers, ACE inhibitors, diuretics, digoxin/digitoxin	Time until first cardiac event	No effect on primary endpoint. May potentially reduce incidence of sudden death in patients with less compromised LVF
Zick *et al.*[7] 2008	Retrospective study on data obtained from the HERB CHF trial (6-month randomized, double-blind, placebo-controlled study) Data analyzed at baseline, 3 and 6 months	WS1442	900 mg (450 mg twice daily)	120	6 months	Stage II–IV NYHA heart failure	ACE inhibitors, ARB, spironolactone, beta-blockers, loop diuretics, thiazide, diuretics, digoxin	Primary goal to measure long term effects of Crataegus preparations	Nominally more heart failure deaths in Crat group (3.3%;2/60 vs 1.6%;1/60) Nominally more hospitalisations in Crat group (18.3%, 11/60 vs 10.0%, 6/60) Less frequent need for diuretic medication amongst Crat group (25% 15/60 vs 31.6% 19/60) Crat group patients 3.9 times more likely to experience heart failure progression event at baseline, risk receding with time to equivalent
Walker and Marakis 2005[53]	Randomized, double-blind, placebo-controlled study	Hawthorn extract (Faros 600 [LI 132, Lichtwer Pharma, Berlin] extract 3:1, standardized to 2.2% flavonoids)	1200 mg bd equivalent to 6 g dried flower tops	80	16 weeks	Type 2 diabetes and hypertension	Diabetic medications, inc. low-dose insulin and hypoglycemic drugs. 71% = hypotensive drugs	Blood pressure Glycemic control	Modest reduction in diastolic BP in hawthorn group.

Table (contd...)

Table 1 (contd...)

Asgary *et al.* 2004[40]	Randomized, double-blind, placebo-controlled trial	Hydroalcoholic extract of Crataegus curvisepal, a flower. 1:8 tincture via percolation	20 drops three times daily	92	More than 4 months	Primary mild hypertension	None	Blood pressure	Significant decrease in both systolic and diastolic blood pressure after third month (p=<0.05)
Habs[34] 2004	Prospective cohort study	WS1442 One cohort on orthodox medication only, the other on Crataegus preparation as add on or monotherapy	Not stated	260 (130 pairs)*	Not stated (commenced in 1999. Results = 2-year interim report. Final results due end of 2004)	Heart failure, stage NYHA II	Standard orthodox medications, including ACE inhibitors, diuretics, beta blockers, and cardiac glycosides	Fatigue Dyspnea Palpitations Nocturia Edema Heart rate Blood pressure Quality of life: Minnesota, living with Heart failure Questionnaire EuroQoL EQ5D	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.
Degenring *et al.*[37] 2003	Randomized, double-blind, parallel group, multicentre, placebo-controlled study	Standardized extract fresh Crataegus berries (Crataegisan)	3 × 30 drops (N = 69) or placebo (N = 74)	143 M = 72 F = 71	8 weeks	Cardiac failure (NYHA class II)	Concomitant medication excluded	Exercise tolerance (bicycle) Blood pressure-heart rate product	Significant improvement in dyspnoea and fatigue.
Tauchert[36] 2002	Randomized, double-blind, placebo-controlled, multicentre trial	WS1442 (dry extract of hawthorn leaves and flowers)	1800 mg or 900 mg or placebo	209 M = 67 F = 142	16 weeks	Chronic congestive heart failure (NYHA class III)	Previously untreated or treated with diuretics and/or low-dose ACE inhibitors	Exercise capacity (bicycle) Subjective symptoms	Improved exercise capacity Symptom reduction
Schroder *et al.*[38] 2001	Multicentre, nonrandomized cohort study	Cralonin (homeopathic preparation)	Cranolin 20 drops tds (80%) or 10 drops tds (15%)	212 110 (Cranolin) 102 (ACE inhibitors)	8 weeks	Mild cardiac insufficiency (NYHA class II)	None	Various, including staircase test, walk test, nocturnal urination, dyspnea.	Crataegus based Cranolin was non-inferior to ACE inhibitor/diuretic treatment in all areas except BP reduction

Table (contd...)

Table 1 (contd...)

Zapfe[33] 2001	Randomized, placebo-controlled, double-blind study	WS1442	240 mg (80 mg tds)	40 WS1442 N = 20 Placebo N = 20	12 weeks	Mild chronic heart failure (NYHA class II)	Cardiovascular medications excluded	Exercise tolerance Double product (heart rate x systolic blood pressure × 10-2)	Improved exercise tolerance Improved oxygen utilisation efficiency of myocardial muscle
Hellenbrecht *et al.*[32] 1990	Randomized, placebo-controlled study	Extract of Crataegus (CRAT) (Kneipp Planzen-Dragees Weissdorn)	3 tid (concentration = not stated)	18 CRAT N = 9 Placebo N = 9	4 weeks	Healthy subjects, challenged with catecholamines	None stated	Various, inc. heart rate and BP before and after exercise	Increased circulatory stress tolerance

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

E monographs specifically approved use of the hawthorn leaf with the flower in the treatment of the decreasing cardiac output as described in functional stage II of NYHA.[43] Findings by Holsbarsch *et al.*[35] suggest that patients with milder forms of heart failure (left ventricular ejection fraction 25–35%) would benefit most from WS1442 in terms of the overall reduction of sudden cardiac death (at the dosage levels used).[44]

The phenomenon of the increased likelihood of patients in the *Crataegus* 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 trial in question was not specifically designed to examine these areas; therefore, other factors might have influenced results and important influences might have been overlooked. The issue of dosage, as discussed above, may be of considerable significance here also, particularly as the study group contained patients suffering from stage IV NYHA heart failure, a group who until now had not been included in clinical trials and who may well be too ill for this treatment to be appropriate. The aldosterone antagonist spironolactone used by some patients in the HRBC CHF trial displays potential for a range of serious side effects, including electrolyte imbalances and hepatotoxicity.[45] The expected incidence of adverse HF events in a patient group of this nature has not been discussed. These data, if available, would be crucial.

The SPICE trial[46] specifically looked at morbidity and mortality as endpoints. The study concluded that the primary endpoints, reductions in cardiac death, nonfatal MI, and hospitalization due to progressive heart failure, were not achieved. The study did find however that deaths of a sudden cardiac cause, deaths due to progressive heart failure, and fatal myocardial infarctions (MI) were all lower in the WS1442 group, although these figures did not reach statistical significance. It was suggested that WS1442 may reduce sudden cardiac deaths in patients with LVEF between 25% and 35%.

Camphor–*Crataegus* combinations have also been used in the treatment of CVD, notably in cases of orthostatic hypotension. Belz *et al.* reported findings of dose-response-related efficacy of a camphor–*Crataegus* product (Korodin) in randomized, placebo-controlled studies.[47] A further study in 2003 suggested that the D-camphor component of this product is responsible for the

rapid initial effect, whereas *Crataegus* berries add a longer lasting pressoric effect.[48] This would confirm the findings of Asgary *et al.* concerning the 3-month time span for pressor effects of Crataregus to become measurable.[40]

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,[49-51] 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.[28,33,36,37,53-55] Daniele *et al.* looked at data from 24 clinical trials and a total of 5577 patients.[56] 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.[36] 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 digitalis medications. Specifically, they examined the potential for acute, coincident illness to engender digitalis 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 Holusbarsh *et al.*[60] 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 cardioactive glycoside medications.[56] 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.[15,25,66-69] 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.*[35] 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 more open-mindedness within the scientific community and a celebration "of the success of bringing different medical cultures together to focus on patients unmet needs." Whole plant hawthorn remedies represent an excellent opportunity for this commendable concept to be taken forward.

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REFERENCES

1. Albarouki E, Peterson A, Molecular and morphological characterization of *Crataegus* L. species (Rosaceae) in southern Syria. Botanical Journal of the Linnean Society; 2007.
2. British, H.F. British Heart Foundation. Statistics. 2006 3rd November; Available from::http://www.heartstats.org/datapage.asp?id=713. [cited in 2007].
3. World, H.O. World Health Organisation Website. Available from: http://www.who.int/topics/cardiovascular_diseasees/en/. [cited in 2007].
4. National S. Heart disease leading cause of death in England and Wales. Health Statistics Quarterly;2006.
5. Herbal Medicines Association, B., British Herbal Pharmacopoeia. Bournemouth: British Herbal Medicines Association;1984.
6. Mills S, Bone K. Principles and Practice of Phytotherapy. London: Churchill Livingstone;2000.
7. Zick SM, Gillespie B, Aaronson K. The Effect of *Crataegus* oxyacantha special extract WS 1442 on clinical progression in patients with mild to moderate symptoms of heart failure. European Journal of Heart Failure; 2008. p. 387-93.
8. American and H. Association. Coronary Risk Profile. Available from: http://www.americanheart.org/presenter.jhtml?identifier=4528. [cited in 2008].
9. Wold RS, Lopez ST, Yau CL, Butler LM, Pareo-Tubbeh SL, Waters DL, *et al*. Increasing trends in elderly persons' use of nonvitamin, nonmineral dietary supplements and concurrent use of medications. J Am Diet Assoc 2005;105:54-63.
10. Miller LG. Selected Clinical Considerations Focussing on Known or Potential Drug-Herb Interactions. Archives of Internal Medicine 1998;158:2200-11.
11. Culpepper N. The British Herbal and Family Physician. Halifax: Nicholson and Co;1820.
12. Kingston R. A phyotchemical 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.
13. Vanhaelen M, Vanhaelen-Fastre R. TLC-densitometric determination of 2,3-cis-procyanidin monomer and oligomers from hawthorn (*Crataegus* laevigata and C. monogyna). J Pharm Biomed Anal 1989;7:1871-5.
14. Kris-Etherton PM, Hecker KD, Bonanome A, Coval SM, Binkoski AE, Hilpert KF, *et al*. Bioactive compounds in foods: their role in the prevention of cardiovascular disease and cancer. Am J Med 2002;113:71-88.
15. Long SR, Carey RA, Crofoot KM, Proteau PJ, Filtz TM. Effect of hawthorn (*Crataegus* oxycantha) crude extract and chromatographic fractions on multiple activities in a cultured cardiomyocyte assay. Phytomedicine 2006;13:643-50.
16. Ling S. Effects of four medicinal herbs on human vascular endothelial cells in culture. Int Jrnl cardio;2007.
17. Brixius K, Willms S, Napp A, Tossios P, Ladage D, Bloch W, *et al*. *Crataegus* special extract WS 1442 induces an endothelium-dependent, NO-mediated vasorelaxation via eNOS-phosphorylation at serine 1177. Cardiovasc Drugs Ther 2006;20:177-84.
18. Quettier-Deleu C, Voiselle G, Fruchart JC, Duriez P, Teissier E, Bailleul F, *et al*. Hawthorn extracts inhibit LDL oxidation. Pharmazie 2003;58:577-81.
19. Zhang Z. Hypercholesterolaemic activity of Hawthorn fruit is mediated by regulation of cholesterol 7 ά Hydroxylase and acyl CoA: cholesterol acyltransferase. Food Res Int 2002;35:885-91.
20. Vierling W, Brand N, Gaedcke F, Sensch KH, Schneider E, Scholz M. Investigation of the pharmaceutical and pharmacological equivalence of different Hawthorn extracts. Phytomedicine 2003;10:8-16.
21. Tsuyaki RT. β-Blockers for congestive heart failure. What is the current consensus? Drugs Aging 2000;16:1-7.
22. Kim SH, Kang KW, Kim KW, Kim ND. Procyanidins in *crataegus* extract evoke endothelium-dependent vasorelaxation in rat aorta. Life Sci 2000;67:121-31.
23. Guo C. Antioxidant activities of peel, pulp and seed fractions of common fruits as determined by FRAP assay. Nut Res 2003;23:1719-26.
24. Zhang Z. Characterisation of antioxidants present in Hawthorn fruits. J Nutr Biol 2000;12:144-52.
25. Bahorun T, Gressier B, Trotin F, Brunet C, Dine T, Luyckx M, *et*

al. Oxygen species scavenging activity of phenolic extracts from hawthorn fresh plant organs and pharmaceutical preparations. Arzneimittelforschung 1996;46:1086-9.

26. Bleske BE. Evaluation of Hawthorn extract on immodulatory biomarkers in a pressure overload model of heart failure. Med Sci Mon 2007;13:255-8.
27. Orhan I. HPLC Quantification of vitexine-2"-O-rhamnoside and hyperoside in three *crataegus* species and their antimicrobial and antiviral activities. Chromato Suppl 2007;66:153-7.
28. Chang WT, Dao J, Shao ZH. Hawthorn: Potential Roles in Cardiovascular Disease. Amer Jrnl Chin Med 2005;33:1-10.
29. Chang Q, Zuo Z, Ho WK, Chow MS. Comparison of the pharmacokinetics of hawthorn phenolics in extract versus individual pure compound. J Clin Pharmacol 2005;45:106-12.
30. Liang M, Xu W, Zhang W, Zhang C, Liu R, Shen Y, *et al*. Quantitative LC/MS/MS method and in vivo pharmacokinetic studies of vitexin rhamnoside, a bioactive constituent on cardiovascular system from hawthorn. Biomed Chromatogr 2007;21:422-9.
31. Pittler MH, Schmidt K, Ernst E. Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials. Am J Med 2003;114:665-74.
32. Hellenbrecht D, Randomised, placebo controlled study with *crataegus* on exercise tests and challenge by catecholamines. Eur J Pharmacol 1990;183:525-6.
33. Zapfe jun G. Clinical efficacy of *crataegus* extract WS 1442 in congestive heart failure NYHA class II. Phytomedicine 2001;8:262-6.
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.
35. Holubarsch CJ, Colucci WS, Meinertz T, Gaus W, Tendera M The efficacy and safety of *Crataegus* extract WS 1442 in patients with heart failure: the SPICE trial. Eur J Heart Fail 2008;10: 1255-63.
36. Tauchert M. Efficacy and safety of *crataegus* extract WS 1442 in comparison with placebo in patients with chronic stable New York Heart Association class-III heart failure. Am Heart J 2002;143:910-5.
37. Degenring FH, Suter A, Weber M, Saller R. A randomised double blind placebo controlled clinical trial of a standardised extract of fresh *Crataegus* berries (Crataegisan) in the treatment of patients with congestive heart failure NYHA II. Phytomedicine 2003;10:363-9.
38. Schroder D, Weiser M, Klein P. Efficacy of a homeopathic *Crataegus* preparation compared with usual therapy for mild (NYHA II) cardiac insufficiency: results of an observational cohort study. Eur J Heart Fail 2002;5:319-26.
39. Furey A, Tassell M. Towards a systematic scientific approach in the assessment of efficacy of an herbal preparation: Hawthorn (*Crataegus* spp.). Eur J Heart Fail 2008;10:1153-7.
40. Asgary S, Naderi GH, Sadeghi M, Kelishadi R, Amiri M. Antihypertensive effect of Iranian *Crataegus* curvisepala Lind: a randomized, double-blind study. Drugs Exp Clin Res 2004;30:221-5.
41. Holubarsch CJ, Colucci WS, Meinertz T, Gaus W, Tendera M. Survival and prognosis: investigation of *Crataegus* extract WS 1442 in congestive heart failure (SPICE)--rationale, study design and study protocol. Eur J Heart Fail 2000;2:431-7.
42. Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. Lancet 1991;337:867-72.
43. ESCOP, Expanded Commision E monographs; 1994.
44. Brown D. High Dose Hawthorn Extract for Advanced Congestive Heart Failure. Herbalgram 2003;57:24-25,28.
45. Association BM. British National Formulary. Mehta DK, editors. 2005.
46. Holubarsch CJ, Colucci WS, Meinertz T, Gaus W, Tendera M The efficacy and safety of *Crataegus* extract WS 1442 in patients with heart failure: the SPICE trial. Eur J Heart Fail 2008;10: 1255-63.
47. Belz GG, Butzer R, Gaus W, Loew D. Camphor-*Crataegus* berry extract combination dose-dependently reduces tilt induced fall in blood pressure in orthostatic hypotension. Phytomedicine 2002. 9: p. 581-588.
48. Belz GG, Loew D. Dose-response related efficacy in orthostatic hypotension of a fixed combination of D-camphor and an extract from fresh *crataegus* berries and the contribution of the single components. Phytomedicine 2003;10:61-7.
49. Yoo KM. Relative antioxidant and cytoprotective activities of common herbs. Food Chem 2007;106:929-36.
50. Cui T, Nakamura K, Tian S, Kayahara H, Tian YL. Polyphenolic content and physiological activities of Chinese hawthorn extracts. Biosci Biotechnol Biochem 2006;70:2948-56.
51. Ljubuncic P, Portnaya I, Cogan U, Azaizeh H, Bomzon A. Antioxidant activity of *Crataegus* aronia aqueous extract used in traditional Arab medicine in Israel. J Ethnopharmacol 2005;101:153-61.
52. Schüssler M, Hölzl J, Fricke U. Myocardial effects of flavonoids from *Crataegus* species. Arzneimittelforschung 1995;45:842-5.
53. Walker AF, Marakis G, Simpson E, Hope JL, Robinson PA, Hassanein M, *et al*. Hypotensive effects of hawthorn for patients with diabetes taking prescription drugs: a randomised controlled trial. Br J Gen Pract 2005;56:437-43.
54. Rigelsky JM, Sweet BV. Hawthorn: pharmacology and therapeutic uses. Am J Health Syst Pharm 2002;59:417-22.
55. Fong HH, Bauman JL. Hawthorn. J Cardiovasc Nurs 2002;16:1-8.
56. Daniele C, Mazzanti G, Pittler MH, Ernst E. Adverse-event profile of *Crataegus* spp.: a systematic review. Drug Saf 2006;29: 523-35.
57. Thorne R. *Crataegus* oxyacantha. Alt Med Rev 1998;3:138-9.
58. Loew D. Phytotherapy in Heart Failure. Phytomedicine 1997;4:267-71.
59. Felker GM, O'Connor CM. Inotropic therapy for heart failure:An evidence based approach. American Heart J 2001;42:393-401.
60. Holubarsch CJ, Colucci WS, Meinertz T, Gaus W, Tendera M. Survival and prognosis: investigation of *Crataegus* extract WS 1442 in congestive heart failure (SPICE)--rationale, study design and study protocol. Eur J Heart Fail 2000;2:431-7.
61. Kernan WN, Castellsague J, Perlman GD, Ostfeld A. Incidence of hospitalization for digitalis toxicity among elderly Americans. Am J Med 1994;96:426-31.
62. Baughman KL, Bradley DJ. Hawthorn extract: is it time to turn over a new leaf? Am J Med 2003;114:700-1.
63. Tankanow R, Tamer HR, Streetman DS, Smith SG, Welton JL, Annesley T, *et al*. Interaction study between digoxin and a preparation of hawthorn (*Crataegus* oxyacantha). J Clin Pharmacol 2003;43:637-42.
64. Kendler BS. Recent nutritional approaches to the prevention and therapy of cardiovascular disease. Prog Cardiovasc Nurs 1997;12:3-23.
65. Spinella M. The importance of pharmacological synergy in psychoactive herbal medicines - Herbal Synergy Review. Alternative Medicine Review; 2002. p. 130-7.
66. Skegert M. Phenols, procyanidins, flavones and flavonols in

some plant materials and their antioxidant activities. Food Chem 2005;89:191-8.

67. Cirico TL, Omaye ST. Additive or synergetic effects of phenolic compounds on human low density lipoprotein oxidation. Food Chem Toxicol 2005;44:510-6.
68. Sokol-Letowska A, Oszmianski J, Wojdylo A. Antioxidant activity of the phenolic compounds of hawthorn, pine and skullcap. Food Chem 2006;103:853-9.
69. Zapatero JM. Selections from current literature: effects of hawthorn on the cardiovascular system. Fam Pract 1999;16:534-8.
70. Cleland JGF. Response from editor to letter to the editor: Alternative approaches to the management of heart failure:Editors response. Eur J Heart Fail 2004;6:517-8.
71. Wojdyto A, Oszmianski J. Influence of polyphenols isoalted from Scutellaria baiacalensis Georgi and *Crataegus* oxyacantha on the oxidative stability of cholesterol in butter stored in various conditions. Euro Food Res Techno 2006;224:635-42.
72. Fan C, Yan J, Qian Y, Wo X, Gao L. Regulation of lipoprotein lipase expression by effect of hawthorn flavonoids on peroxisome proliferator response element pathway. J Pharmacol Sci 2005;100:51-8.

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