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Research Articles

Phytopharmaceutical therapy in cardiovascular disorders:application of and indication for hawthorne today

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Abstract

Hawthorne extracts have been used to support the heart and circulation since about 2000 years. Different species of hawthorne grow all over Europe and are therefore available for production of well-controlled medical preparations standardized to a constant content of oligomeric procyanidines (18,75 %), Crataegus Special Extract WS 1442. This extract may have different potential mechanisms of action explaining the use of Crataegus in different disorders of the heart and circulation. In order to understand the multiple trials conducted with Crataegus, it is important to differentiate between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). Efficacy of Crataegus WS 1442 has been demonstrated in diastolic heart failure (NYHA II) regarding exercise capacity and symptoms. The SPICE trial, conducted in patients with LVEF < 35% (systolic heart failure, HFrEF) and well treated pharmacologically according to guidelines, showed a benefit of the combined endpoint of cardiac death, non-lethal myocardial infarction, and hospitalization, which was – however – not significant. In contrast, secondary endpoints, i.e., cardiovascular death and sudden cardiac death, were significantly reduced over the course of the trial (two years), especially in the subgroub of patients with a LVEF between 25 and 35%. In older days, a smaller trial showed an association between crataegus and less frequent periods of atrial fibrillation and fewer ventricular premature beats. Therefore, there is a good body of evidence that the mechanisms of action of hawthorne, i.e., positive inotropic, antiarrhythmic, antioxydative, as well as coronary vasodilating properties- as shown in animal and in-vitro-studies – work also in patients with HFrEF and HFpEF.

Introduction

Hawthorne, as a phytopharmacon, has been already known and used by roman physicians [1]. In the 16 nth century, Paracelsus – known as a famous doctor in those days – used hawthorne berry wine as a heart supporting medication [1]. In 1896, the first scientific essay was published in the New York Medical Journal dealing with "heart protecting properties".

Mechanisms of action:

1. Positive Inotropism: Using in vitro experiments with isolated failing and non-failing myocardium, crataegus increased force development in muscle strip preparations [2] and extent of shortening of human single myocardial cells [3], (Figure 1).
   In the isolated rat heart, Crataegus extract was shown to increase coronary blood flow by endothelial release of nitric oxide [4].
3. Antiarrhythmic effects were demonstrated for Crataegus WS 1442 in an ischemia-reperfusion model in rats: Ischemia was induced by occlusion of the left coronary artery for seven minutes which was followed by reperfusion due to reopening of the artery. In those animals treated with Crataegus for one week prior to the experiments, incidence of ventricular fibrillation (and therefore mortality) were prevented compared to control animals without pretreatment [5].
4. Crataegus WS 1442 possesses anti-oxidative as well as

anti-inflammatory properties which may be beneficial by preventing progression of coronary heart disease [6].

Sources of Crataegus

The two species - Crataegus oxyacantha and Crataegus monogyna – grow naturally and wildly all over Europe; especially in northern and eastern countries (Figure 2). For commercial purposes, Crataegus species are nowadays grown systematically in agriculture.

Clinical Trials Investigating Crataegus Preparations

Quite recently, heart failure has been divided into three categories mainly according to echocardiographical measurements: Heart failure with reduced left ventricular ejection fraction (lower than 40%, HFrEF, formerly called systolic heart failure), heart failure with LVEF between 40 and 50 % (HFmrEF), and heart failure with preserved ejection fraction above 50% (HFpEF).These new definitions are depicted in Figure 3 [7]. HFmrEF and HFpEF were formerly called diastolic heart failure.

Clinical Trials with Crataegus in Patients with HFpEF and HFmrEF

Firstly, already in 1994, a randomized placebo-controlled double blind study was published in which 72 patients with mild symptoms of heart failure (NYHA II) were treated with Crataegus 900 mg per day versus placebo over a period of 8 weeks. Oxygen consumption was measured before and after treatment: Maximum oxygen uptake as well as oxygen uptake at anaerobic threshold was significantly increased [8]. Thereby, exercise duration until anaerobic threshold was significantly prolonged by 30 seconds in the Crataegus group, whereas not significantly changed in the placebo group (2 seconds), (Figure 4).

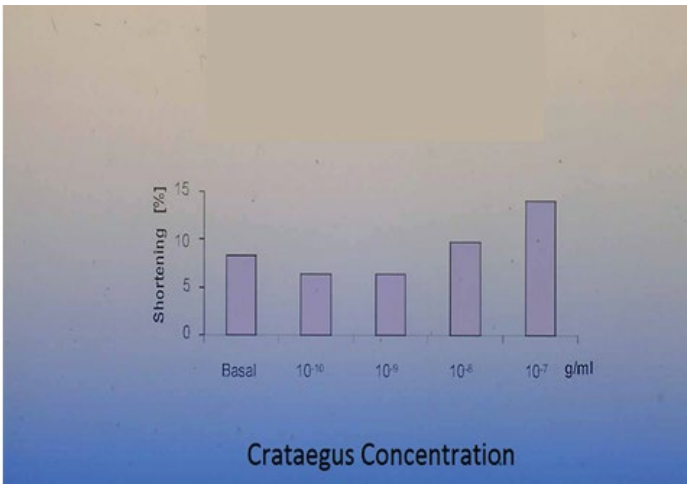

Figure 1. Single muscle cell experiment in human right atrial myocardium. Increase in extent of shorting (% of initial muscle cell length) as a function of crataegus concentration (3).

Secondly, in a meta-analysis performed and published by Pittler and Ernst in 2009, four trials were elected from altogether 29 according to strong scientific criteria like randomization, placebo control, Crataegus extract preparation and dose, as chosen endpoints (exercise capacity). Figure 5 shows this analysis and demonstrates a significant increase in maximum work load by about 7 Watts [9]. Thirdly, and more recently, Crataegus medication was tested during an exercise training program: 140 patients with heart failure [10].

All patients had symptoms NYHA II, LVEF > 40%, NT pro BNP < 450 ng/l and less than two hours of physical exercise training per week. In the placebo group, exercise training alone decreased the time for the 2 km walking test by 1.8 min, in the crataegus group by 2.93 min, a difference which was statistically significant (Figure 6).

Clinical Trials with Crataegus in Patients with HFrEF

The SPICE-Trial: Survival and Prognosis: Investigation of Crataegus Extract WS 1442 in Chronic Heart Failure [11]: The Spice-Trial is the only mortality trial – so far – conducted with a phytopharmacological remedy. 2681 patients with systolic heart failure (LVEF<35%, NYHA II-III, being on standard therapy according to guidelines) were randomized to placebo or Crataegus, and followed up for two years.

Regarding the primary endpoint (cardiac mortality, myocardial infarction, hospitalization for heart failure), there was a tendency for a benefit with Crataegus, which was however not significant (Figure 7). However, regarding secondary endpoints, cardiac mortality was significantly reduced at 6 and 18 months (Figure 8).

Furthermore, in the subgroup of patients with LVEF between 25 and 35%, sudden cardiac death was significantly reduced (Figure 8).

Crataegus oxyacantha

Figure 2. Flowers and leaves of Crataegus oxyacantha.

Table I Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction[c].	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction[c].

Figure 3. Three Categories of Heart Failure: Definitions (7).

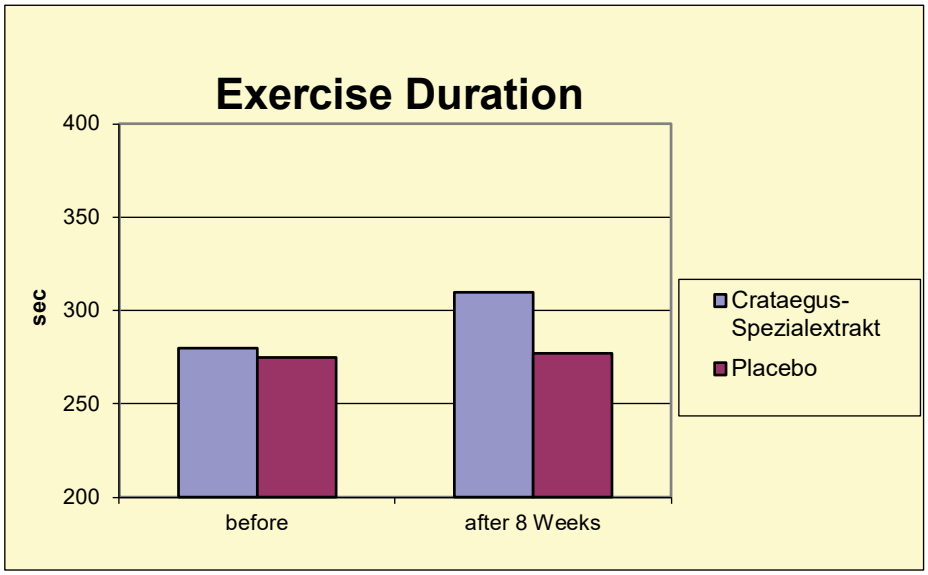

Figure 4. Increase of exercise duration after 8 weeks of treatment with Crataegus special extract as compared to placebo: A randomized, placebo-controlled double-blind trial in 72 patients with heart failure NYHA II (8).

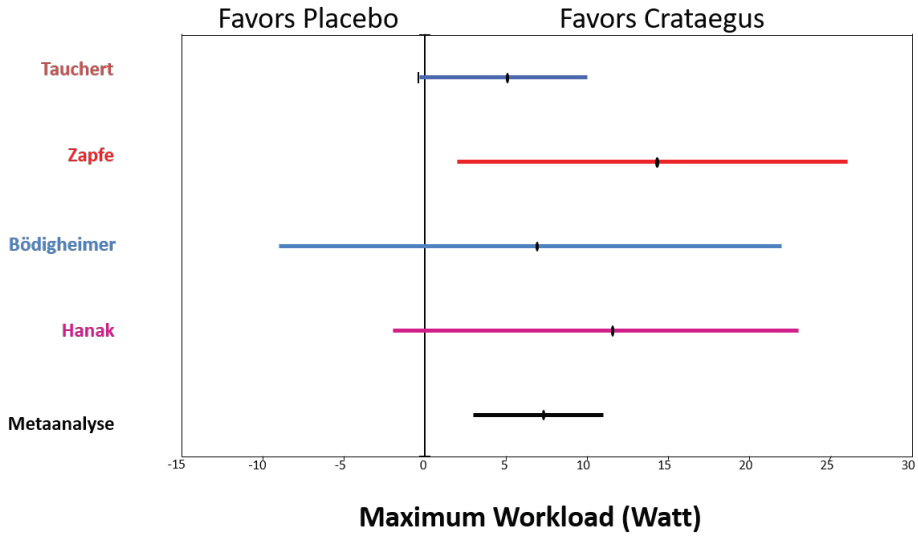

Figure 5. Metaanalysis of maximum workload: Crataegus versus Placebo (9).

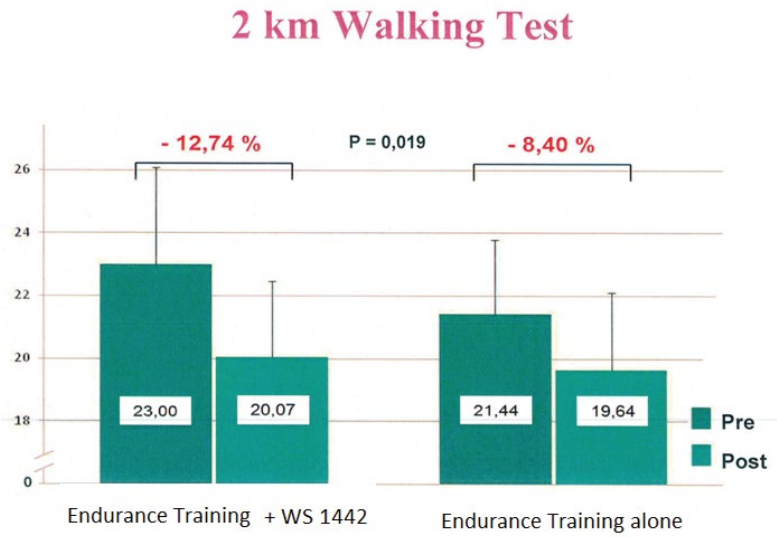

Figure 6. Endurance Training plus WS 1442 versus Endurance Training alone in 140 patients with heart failure with preserved ejection fraction: Time (min) for 2 km walking was significantly decreased with WS 1442 (10).

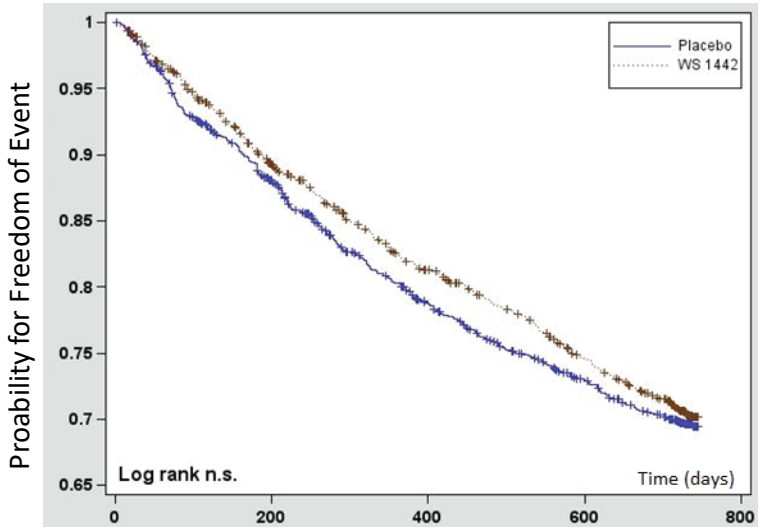

Figure 7. SPICE trial: The composite primary endpoint showed a tendency in favour of Crataegus, which was however not significant (11).

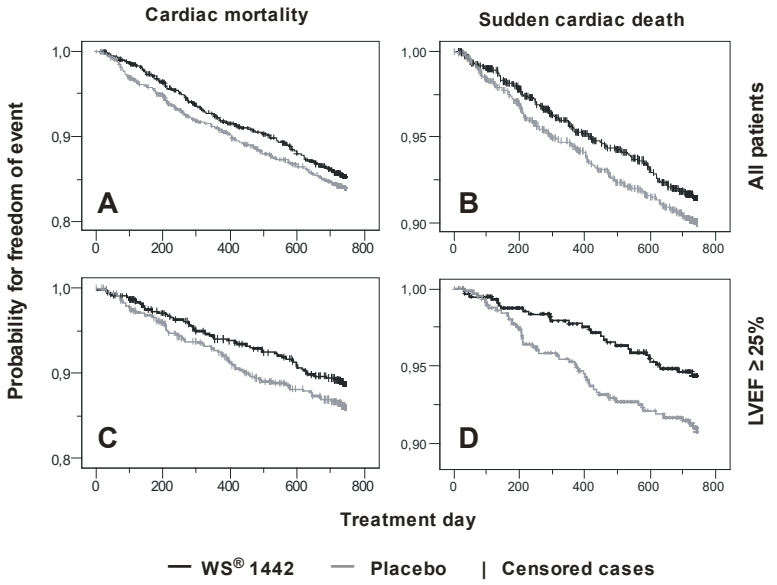

Figure 8. Subgroups of the SPICE trial: Cardiac mortality was significantly decreased in the whole population at 6 and 18 months. Sudden cardiac death was significantly decreased in patients with LVEF >25% and <35% at 12, 18, and 24 months (11).

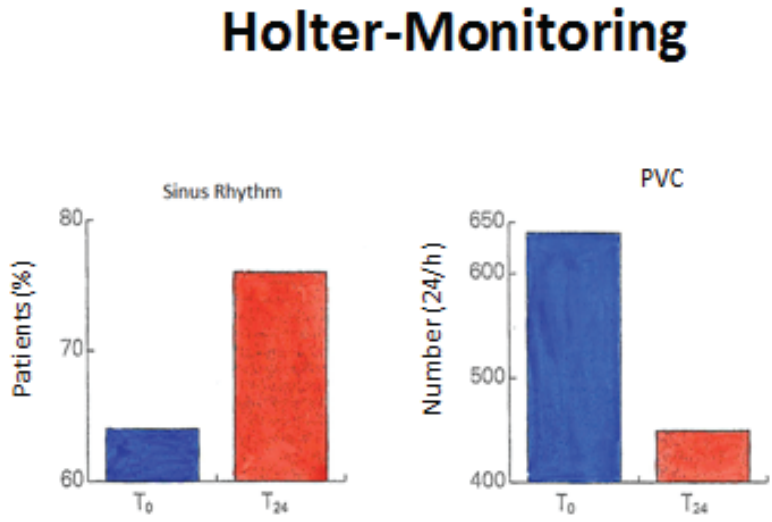

Figure 9. More patients in sinus rhythm and less Premature Ventricular Contractions (PVC) after treatment with Crataegus over 24 weeks [11].

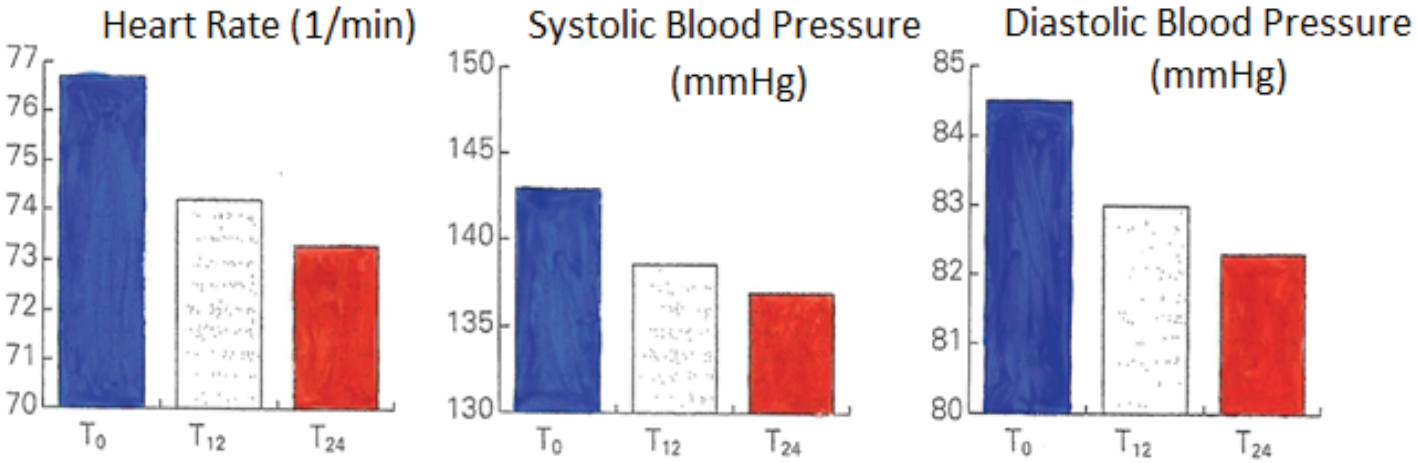

Figure 10. Small decrease of heart rate and blood pressure after treatment with Crataegus over 24 weeks (11).

Cardiac Rhythm Disturbances

Tauchert et al. [12] included 1011 patients with heart failure NYHA II in an observational study over 24 weeks with Crataegus WS 1442 (450 mg twice per day). In 364 patients, Holter-Monitoring was performed at the beginning and at the end of the study. The number of patients with sinus rhythmus at the end of the study was higher than at the beginning. Simultanously, the number of ventricular ectopies decreased by about 30% (Figure 9). Furthermore, in the same trial, there is evidence for a slight effect of Crataegus on heart rate and blood pressure (Figure 10).

Discussion

Taking into account the scientific data and publications mentioned above, the following six different potential indications may be deduced:

1. HFpEF (LVEF>50%): Antihypertensive Therapy plus Crataegus or Crataegus Monotherapy,
2. HFmrEF (LVEF=40-49%): Antihypertensive Therapy plus Crataegus or Crateagus Monotherapy,
3. HFrEF LVEF<40%): Crataegus as Add-on-Therapy to Standard Therapy,
4. Premature Ventricular Contractions LOWN I-IV, if symptomatic,
5. Atrial Fibrillation (in addition to antiarrhythmic therapy),
6. Adjuvant Therapy in Arterial Hypertension.

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