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CRATAEGUS OXYACANTHA - A CARDIOPROTECTIVE HERB

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Abstract: Crataegus oxyacantha Linn., commonly known as Hawthorn, is one of the most widely used herbal heart tonic. Recently it has been extensively investigated chemically and evaluated clinically for its beneficial cardiovascular properties. Hawthorn berries support the heart due to the high content of bioflavonoids. It increases the body's ability to utilize oxygen, and the heart's ability to utilise calcium. The glycero-ethanolic macerate of shoots, leaves and flowers have demonstrated bradycardia, significant decrease of arterial blood pressure, both in normotensive and hypotensive rats and anti-arrhythmic activity in all experimental models of arrhythmia. It has also shown strong negative chronotropic, positive inotropic and coronary dilatating effects in rabbits. The flavanoid present in the extract have shown positive activity in certain microcirculational disturbances in the skin and an inhibitory effect on activity of guinea-pig heart phosphodiesterase. Moreover, it has anti-inflammatory, antioxidant and collagen stabilizing action. Hawthorn is used to treat a wide variety of inflammatory conditions, but primary use is generally restricted to treat hypertension, ischemic heart disease, congestive heart failure and arrhythmia. Investigations all over the world have proved it to be a safe and reliable plant derivative for cardiovascular disorders.

Key words: Ischemic Heart Disease (IHD), Congestive Heart Failure (CHF), PDE inhibitor, Flavonoids, Antioxidant.

INTRODUCTION

Hawthorn, also known as Haw, Hedgethorn, May bush, May blossom, May Day Flower, Ban-sangli (Hindi) and White Thorn; all these names correspond to the genus *Crataegus* (Gr. kratos = hardness of wood), a member of Rosaceae family. It is a spiny tree or shrub, may reach a height of 30 feet, but is often grown as a hedge plant in Europe[1]. In India, it is found in the temperate Himalayas, Kashmir and Himachal Pradesh, at an altitude of 1800-3000 meters[2].

Hawthorn includes the species *C. douglas, C. colombian, C. cuneata, C. laevigata, C. pinnatifida*, and other *Crataegus* species which are used interchangeably with *C. oxyacantha* (Gr. Oxus = sharp, Akantha = a thorn) which is the well known and best studied species. The other species of *Crataegus* (*C. monogyna and C. pentagyna*) have similar pharmacological activities and may be suitable alternatives.

The fruits and flowers constitute a drug which is official in many pharmacopoeias including the Homeopathic Pharmacopoeia of India. The drug from flowers has anti-spasmodic, hypotensive, cardiotonic, diuretic and nervine-sedative properties. Hawthorn is most valuable remedy for cardiovascular system and considered to be one of the best cardiac tonic found in plant kingdom. It dilates peripheral blood vessels, increases metabolism in the heart muscle, dilates coronary vessels and improves blood supply to the heart and thereby help in treating heart disease and mitigating symptoms in early stage of heart failure[3].

Chemical composition[1,4,5]:

1 Vitamin C.
2 Flavonoids : Quercetin, Hyperoside, Rutin, Flavonoglycosyls,Vitexin-4'-rhamnoside.
3 Glycosides.
4 Oligomeric procyanidins (OPC) - epicatechol.
5 Anthocyanidins and Proanthocyanidins (biflavans)
6 Saponins and Tannins.
7 Cratetegin (most prevelant in flowers > leaves > berries).
8 Other chemical constituents: a) Cardiotonic amines : Phenylethylamine, Tyramine, Isobutylamine, O-methoxy phenylethylamine; b) Choline and acetylcholine; c) Purine derivatives : Adenosine, Adenine, Guanine, Caffeic acid; d) Amygdalin; e) Pectins; f) Triterpene acids : Ursolic acid, Oleonic acid, Crategolic acid.

Pharmacological properties

Various hawthorn preparations have been studied for their pharmacological properties with the research primarily focusing on the herb's cardiovascular activity. The majority of the recent clinical studies have conducted using proprietary preparations prepared from the leaves and flowers. Other preparations used include fresh flower/leaf/fruit combinations as well as aqueous, methanolic and ethanolic extracts[6].

Each hawthorn preparation has a number of active compounds, and no single constituent has proven to be the primary agent for the effect observed. Among the active constituents identified, the most important are the phenols, specifically the flavonoids and the oligomeric procyanidins (OPC) fractions derived from the catechin and epicatechin chemical units. Numerous studies have also been conducted using isolated compounds giving a similar pharmacodynamic profile. Cardioactivity has been observed *in vitro* and in animal and human clinical trials. In general, preparations administered orally are reported to have more prolonged effect than those administered parenterally[7].

A. Cardiovascular effects: The primary activity of hawthorn is to increase coronary blood flow[8]. This may be due to relaxation of coronary arteries, which directly increases blood flow or through an increase in contraction and relaxation velocities, which increases the diastolic interval and thus allows more time for blood passage through the coronary arteries[9].

Hawthorn's positive inotropic action may also be due to inhibition of myocardial Na^+/K^+ ATPase which is an integral membrane enzyme that maintains cardiac resting potential[10]. It also decreases blood pressure which results in an increase in exercise tolerance during the early stage of congestive heart failure (CHF)[11]. Surprisingly, Hawthorn has the ability to regulate both low and high blood pressure. With the bioflavanoids reportedly dilating both peripheral and coronary blood vessels leading to its use in angina[12]; the procyanidins content is claimed to support the vasorelaxant effects[13]. Hawthorn's glycoside component has also been reported to increase vagal tone of the heart[14].

One mechanism, commonly proposed for its cardioactive effect is its ability to inhibit the enzyme phosphodiesterase (PDE) which ultimately results in an increase in intracellular cyclic nucleotides and a subsequent positive inotropic effect[15].

Interestingly, catechin, the flavonoid vitexin and flavonol kaempferol from hawthorn were observed to be structurally similar to papaverine and theophylline, the two chemical agents known to inhibit PDE. Another constituent of hawthorn, ursolic acid has also been reported to interact with the digitaloid binding site for Na^+/K^+ ATPase[6].

Hawthorn has also been reported to have angiotensin converting enzyme (ACE) inhibiting effect[16,17]. It may also have a cardio-protective effect due to its ability to decrease the oxygen demands of cardiac tissue[18,19]. Varying results have been observed regarding the effect of hawthorn and its constituents on heart rate. In majority of *in vitro* studies, an increase in heart rate has been observed while conversely, most *in vivo* studies report a decrease in heart rate[7].

B. Other pharmacological effects: Hawthorn has been shown to exhibit antioxidant activity associated with its flavanoid and procyanidin content. The most significant antioxidant activity was observed using an extract of fresh, young leaves followed by fresh floral buds and dried flowers[20]. Hawthorn reportedly has the ability to increase intracellular vitamin C and has a protective effect on oxidative processes[21]. The free radical scavenging activity contributes to hawthorn's cardio-protective effect after ischemia and this property is primarily correlated with the oligomeric procyanidins[22].

Hawthorn also exhibits anti-inflammatory property by preventing synthesis and release of inflammatory promoters such as histamines, serine proteases, prostaglandins, leukotrienes etc. as well as inhibiting enzymatic cleavage by enzyme secreted by leukocytes during inflammation[23].Not only this, *Crataegus* also have significant collagen stabilising

action by affecting collagen metabolism. It cross links collagen fibres to reinforce the collagen matrix of connective tissues[1].

Mild to moderate sedative effect has been demonstrated in humans and animal studies with hawthorn constituents and OPC'S are reported to be partially responsible for this effect[24,25].

In a nut shell, hawthorn's flavans, by inhibiting phosphodiesterase, have a positive effect on myocardium's calcium metabolism resulting in an increase in contractile power (positive inotropic effect) and promoting normal rhythm. It does inhibit angiotensin converting enzyme (ACE). Its free radical scavenging capacity further protects myocardium particularly during ischemic situations. Hawthorn's anti-inflammatory and collagen stabilizing properties are additional advantages of its therapeutic application.

Animal Experimental Studies: Hawthorn has been extensively studied scientifically regarding its pharmacological properties with reference to cardiovascular benefits in various animal experimental studies. Most of the work has been carried out in Germany, Italy, Hungary and Russian and very few from South-East Asia. It will not be therefore inappropriate to mention few of the pertinent studies unveiling the underlying pharmacological mechanisms.

The Hawthorn extract LI 132 prepared from leaves and flowers and standardised to 2.2% flavonoids was investigated for its effect on contraction, energy turnovers and apparent refractory period of isolated cardiac myocytes from adult rats. It exhibited a positive inotropic effect on the contraction amplitude accompanied by a moderate increase of energy turnover, both for mechanical and ionic processes[26].

Oral administration of a fraction of *Crataegus* (*Oligomeric procyanidines*) led to a significant dose dependent rise in blood flow in the myocardium of the left ventricle in unanesthetized dogs, for several hours measured by chronically implanted heat-conduction probes. The highest increase was reaching an average value of about + 70% of the resting flow[27]. Administration of oral standardized hawthorn extract to an ischemic/reperfusion rat model effectively protected animals from reperfusion induced arrhythmias mortality and hypotensive crisis. These findings may indicate uses of hawthorn not only in early but also in advanced stages of heart failure and for secondary prevention after myocardial infarction[28].

The effect of pre-treatment with the powder of *C. oxyacantha* on the release of lactate dehydrogenase (LDH) during ischemia and reperfusion was also studied in isolated rat heart model. Attenuation of LDH release by *Crataegus* pre-treatment suggests a preservation of cell membrane and a protection from myocardial damage[29].

Jayalakshmi and associates investigated the effect of alcoholic extract of *Crataegus oxyacantha* (AEC) on mitochondrial function during experimentally induced myocardial infarction in rat. AEC was administered orally (0.5 ml/100g BW/day) to male albino rats (150-200 g) for 30 days. At the end of the experimental study, the animals were administered isoproterenol (85 mg/kg BW, S.C.) for 2 days at an interval of 24 hrs. AEC pre-treatment maintained mitochondrial antioxidant status, prevented mitochondrial lipid peroxidative damages and decreased in Kreb's cycle enzymes induced by isoproterenol in rat's heart[30]. Hawthorn extract induced concentration dependent relaxation of the U46619 - pre contracted rat artery with an LC_{50} of 0.22±0.02 mg/ml. Removal of functional endothelium reduced by approximately 85 percent of maximum relaxant response to hawthorn extract[31].

The influence of WS(R) 1442, a special extract of *Crataegus* leaves with flowers, on the relaxation of rat aorta and human mammalian artery (coronary bypass patients) has been recently investigated. The study concludes that WS 1442 induces an endothelium - dependent, NO-mediated vasorelaxation via eNOS phosphorylation at serine 1177[32].

Tincture of *Crataegus* (TCR), an alcoholic extract of the berries of *C. oxyacantha*, when administered to rats fed with a hyperlipidemic diet, could prevent the elevation in plasma lipid levels. A significant decrease in lipid deposits in liver and aorta was also observed[33]. Not only this, but TCR significantly increased the binding of 1251 - LDL to the liver plasma membrane, in-vitro, indicating an enhancement in the LDL receptor activity. It also showed increased bile acid excretion and decreased hepatic cholesterol synthesis in atherogenic diet fed rats. The various constituents of TCR - flavonoids, triterpene and saponins and a few cardioactive amines - may act synergistically to bring about the observed effects[34]. Proanthocyanidins may actually reverse atherosclerosis plaque in laboratory studies[35].

Clinical studies: Hawthorn is currently used extensively by physicians in Europe in its standardized form for early stage of heart failure which consists

of class I and class II cardiac insufficiency as classified by New York Heart Association (NYHA) and various other cardiovascular and peripheral circulatory conditions including angina, cardiac incompetence not yet requiring digitalis, hypertension, arrhythmias etc[28,36,37].

In one clinical study, the effect of 200 mg three times a day administration of a proprietary methanolic extract adjusted to 18mg flavanoids was tested on 78 patients with NYHA class II heart failure. It was a multicentric, double blinded, placebo-controlled study on exercise ability as tested by ergometer bicycle. Median value of work capacity increased in hawthorn group but not in placebo group. Systolic blood pressure and heart rate were significantly decreased in hawthorn group compared to placebo group[38].

In another double blind cross over study, 36 patients with multiple co-morbidities were tested for the effect of proprietary ethanolic extract containing 18.75 per cent proanthcyanidins. The patients treated with hawthorn showed a decrease in heart rate, improvement in cardiac out put under resting and exercise conditions. Treated patients also had significant improvement in psychological assessment including a reduction in anxiety and improvement in sleep pattern[39].

In one multicentre, double-blind study, a standardized hawthorn extract compared favourably to captopril. 37.5 mg daily, in the treatment of 132 individuals with NYHA class II cardiac insufficiency. Both the drugs reported to reduce peripheral blood flow resistance but hawthorn had added advantage over captopril of being a cardio-tonic agent also[40].

We have also observed blood pressure lowering effect of *Crataegus* in patients with stage 1 and 2 hypertension of JNC VII. The mother tincture of *Crataegus* was administered in the dose of 10 drops in half cup of water three times a day for four weeks. *Crataegus* caused a significant ($p<0.02$) decrease in mean systolic blood pressure and also decreased significantly ($p<0.01$) the mean diastolic blood pressure in patients with stage 1 hypertension. However, there was no significant alteration in mean systolic and diastolic blood pressure in patients of stage 2 hypertension (Unpublished data).

Recently, a randomised controlled trial has demonstrated a hypotensive effect of hawthorn in patients with diabetes taking prescription drugs[41]. A review of 15 human clinical trials on 872 patients using standardized hawthorn supplements has been described[15].

Therapeutic indications: With the available experimental work and clinical research Crataegus's primary use has been recommended in the following cardiovascular conditions:

1. Hypertension
2. Angina
3. Arrhythmias
4. Congestive Heart Failure (NYHA class I & II)
5. Peripheral vascular disorders
6. Antioxidant and lipid regulating agent.

Recommended dosage[42]: Most of the available hawthorn preparations have been standardized to 2% vitexin and/or 20% procyanidins per dose. European products are standardized to 2.2% flavonoids. Most of the preparations are available as dietary supplements. However, for the purpose of therapy, the most common dosage recommendations are:

1. Standardized extract - 250 mg three times a day.
2. Berry - 300 mg three times a day.
3. Tincture - 1 ml three times a day.
4. Crude - 200 mg daily.
5. Leaf and flower extract - 160 mg = 3.5 mg flavonoids daily.

Toxicity, Teratogenicity and drug interactions: Hawthorn is safe and its side effects are minimal when consumed in recommended dosages. No changes in blood status, liver enzymes, electrolytes, and glucose or erythrocyte sedimentation rate were observed in a human clinical study of 136 patients treated with 160 mg of the WS 1442 hawthorn extract[37].There are no reports of adverse effects with low doses but higher doses increase the risk of drug induced hypotension and sedation. It should not be used in children under 2 years of age[42].

General symptoms of acute toxicity observed in a number of animal models (e.g. guinea-pig, frog, tortoise, cat, rabbit and rat) have been documented as bradycardia and respiratory depression leading to cardiac arrest and respiratory paralysis[43-45].

A recent, systemic review is available regarding adverse event profile and safety data of all available human studies on hawthorn mono preparations. Twenty nine clinical studies were identified of which 24 met the inclusion criteria of the study. A total of 7311 patients were enrolled, and data from 5577 patients were available for analysis. The daily dose and duration of treatment ranged from 160 to 1800 mg and from 3 to 24 weeks respectively. The extracts most used in the clinical trials were WS 1442 (Standardized to 18.75 % oligomeric procyanidins) and LI 132 (Standardized to 2.25 % flavanoids).

Overall, 116 adverse events were reported most of which were, in general, mild to moderate. Eight severe adverse events were reported with the LI 132 extract. The most frequent adverse events were dizziness/ vertigo (n=15), gastrointestinal complaints (n=24), headache (n=9), migraine (n=8) and palpitation (n=11).

The WHO spontaneous reporting scheme receives 18 case reports. The most frequent adverse events were dizziness (n=6), nausea (n=5), fall (n=2), gastro intestinal haemorrhage (n=2), circulation failure (n=2) and erythematous rash (n=2). There were no reports of drug interactions[46]. Hawthorn however, should not be used, preferably in pregnancy because of its demonstrable action on uterus (reduced tone and motility) *in vivo* and *in vitro*[43-45].

Hawthorn interactions are likely with agents that have an effect on the cardiovascular system. It has shown synergy with digitalis by enhancing the effect of cardiac glycosides. This effect is thought to be due to an inhibitory effect on cAMP-PDE and thus effects on calcium channels[47]. Use of hawthorn with β-blockers may bring about a mild rise in blood pressure in hypertensive patients, as β-blockers decrease cardiac out put in such patients. However, no significant disease state interactions have been reported. Patients with cardiovascular disease or those who are using cardiovascular medications should inform their treating physicians regarding their consumption of hawthorn preparations[4].

Conclusion: *Crataegus oxyacantha* is characterized by its phenolic constituents, in particular, the flavonoid components, to which many of the pharmacological properties have been attributed. Pharmacological actions documented in both animal and human studies support the traditional actions of hawthorn and include cardioactive, hypotensive and coronary vasodilator, with few minor side effects. On account of its efficacy and safety hawthorn has made its place in British pharmacopoeia, European pharmacopoeia and Homoeopathic materia and medica. The German Commission has also approved the use of hawthorn as a heart remedy. The time is not too far, when hawthorn will be a part of standard prescription for the common cardiovascular disorders.

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