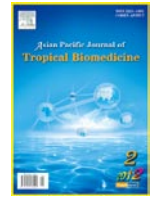




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## Ethnomedicinal and phytopharmacological potential of *Crataegus oxyacantha* Linn. – A review

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### ABSTRACT

Traditional herbal medicines are practiced in the entire world and their ethnopharmacological records reveal that most of the people of the world have been using plants, animals, micro-organisms and minerals for treating various diseases. *Crataegus oxyacantha* (*C. oxyacantha*) Linn. (Rosaceae) commonly known as Hawthorn is an official plant in Homeopathic System of Medicine to treat various conditions of cardiovascular system. In recent times, this drug has been subjected to phytochemical, pharmacological, pre-clinical and clinical investigations and many new investigations have been indicated. Current review finds ethnomedicinal and phytopharmacological potential of leaves, flowers, berries, bark *etc.* for exploring the immense medicinal potential of Hawthorn. At the same time, studies to evaluate the dosage, toxicity and interactions with drugs and herbs on simultaneous use, which is imperative for optimal and safe utilization of this plant, are explained. There are few comprehensive reports available on clinical use of Hawthorn in chronic heart failure patients have shown promising results.

### 1. Introduction

Genus name *Crataegus* is derived from Greek words *Kratos* meaning hardness of wood<sup>[1]</sup> and mostly lies between latitudes 30° and 50° N. *Crataegus* is a large genus of trees and shrubs in the rose family, Rosaceae with about 250 currently recognized species native to northern temperate zones<sup>[2,3]</sup>. *Crataegus oxyacantha* (*C. oxyacantha*) Linn. is an official plant in homeopathic system of medicine, traditionally employed as a cardioprotective<sup>[4,5]</sup>.

Vernacular names:

English: Hawthorn, May thorn, May blossom

Hindi: Vansaangli

Local name: Pandaakh

### 2. Morphological description

Species name *Oxyacantha*, is derived from the Greek words *oxus* meaning sharp, and *akantha* meaning a thorn. It is small to medium sized deciduous tree in Rosaceae with

umbrella shaped clusters of white or pink flowers, glossy-green toothed leaves and bright shiny red berries. White coloured flowers are borne in flat-topped inflorescences termed corymbs or in globular inflorescences termed umbels and usually contain 5 petals, 5 to 18 stamens and have a rancid odour. *Oxyacantha* fruits (Figure 1) are known as pomes, although the seeds and their bony endocarps are termed pyrenes. Between 1 and 5 pyrenes are produced in each pome. The calyx is persistent at the top of the fruit. The thorns are small sharp-tipped branches that arise either from other branches or from the trunk, and are typically 1–3 cm long. *Oxyacantha* trunk or stem has hard wood, smooth and ash-gray bark and thorny branches<sup>[8, 9]</sup>.

Kingdom: Plantae  
Division: Angiospermae  
Class: Magnoliopsida  
Order: Rosales  
Family: Rosaceae  
Sub-family: Maloideae  
Tribe: Crataegeae  
Genus: *Crataegus*  
Species: *Oxyacantha*



**Figure 1** Taxonomic classification of *Crataegus oxyacantha* Linn<sup>[6,7]</sup>

### 3. Habitat

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These small to medium sized trees (5–15 m tall) are grown as a hedge plant in Europe, and found mostly in temperate areas like North America, Western Asia, India, China and North Africa. In the 1800's, British settlers introduced it into Tasmania and other parts of Australia as a hedge plant, and it now runs wild in Victoria, Tasmania, the Adelaide Hills and the tablelands of New South Wales. *Crataegus* is an aggressive settler that is tenacious and difficult to remove; it has been declared a baneful weed in many Australian states. In India, it is found in the temperate Himalayas, Kashmir and Himachal Pradesh, at an altitude of 1 800–3 000 meters [2, 8, 10, 11].

#### 4. Ethnobotanical use

*C. oxyacantha* is a fruit-bearing plant with a long history as a pharmacological active therapeutic substance. It has been used traditionally as a cardiac tonic and current uses include treatment for angina, hypertension, arrhythmias, congestive heart failure [12]. Popular Chinese drink shan zha containing active therapeutic principles of Hawthorn has been used in lowering blood lipid levels in humans and rats [13]. *C. oxyacantha* (Aubepine, Hawthorn), was used by European herbalist in the first century A.D [14]. Hawthorn has an engrossing history of use and it also was considered as sacred by many traditions. The flowering branches of hawthorn tree heralded the beginning of ancient Celtic festival of Beltane and for this reason it was also called the May-flower. In Celtic tradition, Hawthorn tree represented the Goddess and was surrounded by faeries and elemental spirits [15]. A well-known physician, **the late Dr. Green, of Ennis, County Clare, Ireland**, attained a reputation in the treating various ailments of heart, keeping the remedy a mystery. Upon his death, in 1894, his daughter revealed the fact that this famous cure was a tincture of the ripe berries of *C. oxyacantha*. In Oriental medicine the fruits are considered to have sour, sweet, slightly warming qualities. A number of North American hawthorns were used as medicine by indigenous groups [16]. Other uses of hawthorn have included in the treatment of digestive ailments, dyspnea, kidney stones. Today, hawthorn is used primarily for various cardiovascular conditions but it is yet to be entered in India as cardiac tonic [17].

#### 5. Phytochemistry

*C. oxyacantha* Linn. contains heptahydroxy flavan glycoside, flavan polymers [18,19]. The flavonoid components and oligomeric procyanidins, as the key constituents of *C. oxyacantha*, are responsible for its therapeutic potential [10]. They are present in leaves, flowers and berries. The main phytoconstituents of *C. oxyacantha* Linn. have been mentioned in Table 1 given below.

#### 6. Pharmacological activities

The red fruit is rich in bioflavonoids and is the most common part employed in herbal medicine. Various extracts of *C. oxyacantha* Linn. are evaluated for screening *in-vitro*/*in-vivo* models. In experimental studies, hypolipidaemic, anti-inflammatory, antianxiety activity of the berries of *C. oxyacantha* have been confirmed [24–26]. Bioflavonoids of *oxyacantha* relax and dilate the arteries, especially the coronary arteries. This increases the blood flow of heart muscle and reduces the symptoms of angina and contractions of the heart muscle [23]. The bioflavonoids are also strongly antioxidant, helping to reduce degeneration of blood vessels [47–50]. Various pharmacological activities of *C. oxyacantha* Linn. have been mentioned in Table 2.

#### 7. Anti-arrhythmic activity

This activity was estimated using a cultured cardiomyocyte assay method. Ethanolic extract of *C. oxyacantha* was compared with other known cardioactive drugs (ouabain, epinephrine, milrinone and propranolol). *C. oxyacantha* extract appeared to be capable of inducing rhythmicity in quiescent cardiomyocytes and showed antiarrhythmic potential along with negative chronotropic effects but did not cause  $\beta$ -adrenergic receptor blockade [35].

#### 8. Myocardial infarction

In a study the endothelium-dependent relaxation elicited by procyanidins fractionated from *C. oxyacantha* extract was investigated in isolated rat aorta. The extract of *C. oxyacantha* relaxed vascular tone or increased production of cyclic GMP in the rat aorta which suggested the cardioprotective potential of *C. oxyacantha* [40]. A study was done to investigate the effect of the alcoholic extract of *C. oxyacantha* on mitochondrial function during experimentally induced myocardial infarction in rats. Alcoholic extract was administered orally to male albino rats at a dosage of 5  $\mu$  L/g b.w. per day for 30 days. At the end of the experiment period, the animals were administered isoproterenol (85  $\mu$  g/g b.w., s.c.) for 2 days at an interval of 24 h. After 48 h, the rats were anaesthetized and sacrificed. The hearts were homogenized for biochemical and electron microscopic analysis. Pretreatment with the alcoholic extract maintained mitochondrial antioxidant status, decrease the Krebs' cycle enzymes induced by isoproterenol in rat heart and prevented mitochondrial lipid peroxidative damage [34]. In another study the effect of the pretreatment with the powder of *C. oxyacantha* on the release of lactate dehydrogenase (LDH) during ischemia and reperfusion was studied in an isolated rat heart model. The attenuation of the LDH release by *C. oxyacantha* pretreatment suggested a preservation of the cell membrane and a protection from myocardial damage [48].

## 9. Myocardial ischemia

In a study the protective effect of dried extract of *C. oxycantha* against reperfusion arrhythmias pretreatment was investigated with the Langendorff heart of the rat after global no-flow ischemia. *C. oxycantha* pretreatment significantly reduced the average prevalence of malignant arrhythmias<sup>[49]</sup>. Another study was conducted to evaluate the efficacy and mechanism of *C. oxycantha* extract in preventing ischemia-reperfusion injury in an *in vivo* rat model. *C. oxycantha* extract at 100  $\mu$ g/g b.w. showed a significant decrease in creatine kinase activity and infarct size. At the molecular level, *C. oxycantha* administration resulted in a significant attenuation of phosphatase and tensin homolog deleted on chromosome and upregulation of phospho-Akt and c-Raf levels in the heart and this suggested that *C. oxycantha* extract attenuated apoptotic incidence in the experimental myocardial ischemia-reperfusion model by regulating Akt and hypoxia-inducible factor (HIF-1) signaling pathways<sup>[37]</sup>.

**Table 1**

Phytoconstituents of *C. oxycantha* Linn.

Plant part	Compound name	Research area	Year	Reference
REPOTED DATA				
Fruits, Leaves	Heptahydroxyflavan glycoside	Germany	1955	[18]
Fruits, Leaves	Flavan polymers	Germany	1967	[19]
Leaves, Flowers	Monoamines noradrenaline, adrenaline, dopamine and L-DOPA	Italy	2007	[20]
Leaves, Fruits	Procyanidins	Poland	2007	[21]
Leaves, Flowers	Flavonoids such as vitexin-2''-O-rhamnoside, hyperoside and oligomeric procyanidins	Italy	2007	[22]
REVIEWED DATA				
Fruits, Flowers, Leaves	Isobutylamine, O-methoxy phenylethylamine, Ursolic acid, Oleanolic acid, Crategolic acid, Adenosine Adenine, Guanine, Caffeic acid, Quercetin, Hyperoside, Rutin, Vitamin C, Vitexin-4'-rhamnoside, epicatechol, Tyramine	India	2007	[10]

**Table 2**

Pharmacological activities *C. oxycantha* Linn.

Part used	Extraction method	Extract	Biological Activity	Research area	Year	Reference
Leaves	Percolation	Aqueous	Hypotensive	West bank	1987	[27]
Berries	Percolation	Alcoholic	Hypolipidemic	India	1994	[28]
Bark	Hot extraction	Acetone $\rightarrow$ ethyl acetate	Antioxidant	Portugal	2000	[29]
Entire plant	86% maceration	Alcohol	Hypotensive	Johannesburg	2000	[30]
Leaves, berries	Percolation	Methanol	ACE inhibitors	France	2001	[31]
Berries	Hot extraction	49% ethanol	Cardioprotective	Switzerland	2003	[32]
Leaves, berries	Percolation	Alcoholic	Anxiety and depression	France	2004	[33]
Leaves	Hot extraction	50% ethanol	Negative chronotropic effect, cardiotoxic	USA	2006	[34]
Berries	Cold percolation	95% ethanol	Myocardial infarction	USA	2006	[35]
Flowers	Percolation	81% Hydro alcoholic	Antioxidant	Poland	2007	[21]
Berries	Triple percolation	70% ethanol	Free-radical-scavenging, anti-inflammatory, gastro protective, antimicrobial activities	Serbia	2008	[24]
Berries	Percolation		Hypolipidemic and antioxidant	India	2008	[36]
Leaves, berries, flowers	Percolation		Cardioprotective	USA	2008	[25]
Flowers	Percolation	Alcoholic	Inhibition of thromboxane A2	USA	2010	[37]
Leaves, berries	Maceration	Alcoholic	Immunomodulatory	India	2010	[38]
Entire plant	Hot extraction	Methanol	Hypolipidemic	Morocco	2011	[39]

## 10. Congestive heart failure

A placebo controlled, randomized, parallel group, multicentre trial conducted, showed the efficacy and safety of a standardized extract of fresh berries of *C. oxycantha* L. and *C. monogyna* Jacq. (Crataegisan<sup>®</sup>) in patients with cardiac failure NYHA class II. In this study, a total of 143 patients were treated with 3 times 30 drops of the extract or placebo for 8 weeks. The results showed a significant improvement in their heart failure condition under long term therapy with the standardized extract of fresh *C. oxycantha* berries <sup>[32]</sup>.

## 11. Anti-inflammatory, gastroprotective, antimicrobial

Study was carried out to test free radical scavenging, anti-inflammatory, gastroprotective, and antimicrobial activities of *C. monogyna* and *C. oxycantha*; syn. *C. laevigata*. The

free-radical-scavenging activity exhibited by the total phenolic content was evaluated by using DPPH radical-scavenging assay method. For determination of anti-inflammatory activity of *C. oxyacantha*, oral administration of extract caused dose-dependent effect in a model of carrageenan-induced rat paw edema. Hawthorn extract also produced dose-dependent gastroprotective activity, with the efficacy comparable to that of the ranitidine (reference drug). This activity of the extract was examined using an model of ethanol-induced acute stress ulcer in rats. The active components identified in the extract might be responsible for antimicrobial potential of the extract which was investigated against Gram-positive bacteria *Micrococcus flavus*, *Bacillus subtilis*, and *Lysteria monocytogenes* and *Candida albicans* which divulged its bactericidal activity[24].

## 12. Anxiety and depression

A large randomized controlled trial found that a combination of *C. oxyacantha*, *Eschscholzia californica* and magnesium was more effective than placebo in reducing anxiety in 264 individuals with generalised anxiety disorder[33]. Another study evaluated for the central effects of the phytotherapeutic product-CPV (dry extract of *C. oxyacantha*, *Passiflora incarnata* and *Valeriana officinalis*) in animals models. Evaluation of anxiolytic effect of this extract on the elevated plus-maze (EPM) was carried out in order to investigate the psychopharmacological profile of CPV extract and the result indicated antianxiety potential of extract[50].

## 13. Antioxidant

For antioxidant activity estimation polyphenolic preparations containing oligomeric procyanidin from the bark of common pine (*Pinus sylvestris* L.) and hawthorn (*C. oxyacantha* L.) and flavones of skullcap (*Scutellaria baicalensis* Georgi) roots were employed. Multicomponent mixtures were fractionated and the antioxidant activity of fractions was tested *in vitro* with linoleic acid oxidation by AAPH-generated radicals. All preparations at 6 and 12 ppm concentrations exhibited protective activity, from 45% to 95% in relation to the control sample[21]. In another study the antioxidant capacity of extracts of *C. oxyacantha*, *Hamamelis virginiana*, *Hydrastis canadensis* has been investigated. The total antioxidant activity conferred by all hydrogen donating antioxidants present in these extracts has been assessed by the ABTS assay and the result indicated the antioxidative potential of extracts[29].

## 14. Refractory hypertension

The hypotensive effect of *C. oxyacantha* was examined *in vivo* using normal anaesthetized rats. An aqueous extract

of *C. oxyacantha* leaves was found to produce a significant decrease in the systolic, diastolic and mean blood pressure at a dose of 31 mg/kg. In another study efficiency of *C. oxyacantha* in the treatment of refractory hypertension in adult males was measured and the result indicated that *C. oxyacantha* Linn. has mild antihypertensive properties[30].

## 15. Hypolipidemic activity

Tincture of Crataegus (TCR) when administered to rats fed a hyperlipidemic diet (HLD), could prevent the elevation in plasma lipid levels. A significant decrease in lipid deposits in liver and aorta was also observed. Analysis of the plasma lipoprotein profile showed that TCR produced remarkable reduction in the increased levels of cholesterol, triglycerides and phospholipids in the low density lipoprotein (LDL) and very low density lipoprotein (VLDL) fractions in hyperlipidemic rats. Histological examination showed severe fatty vacuolation and degeneration of liver of HLD fed rats. TCR administration had an ameliorating effect on these changes[28] and when TCR and *Mangifera indica* extract was synergistically supplied to atherogenic rats significantly decrease lipid accumulation in the liver and aorta reverting the hyperlipidaemic condition of these rats[36]. In another study effect of methanolic extract of *C. oxyacantha* was being determined and it was found that the serum cholesterol, triglycerides and glucose levels and the count of leukocytes and platelets decreased significantly[39].

## 16. Angiotensin converting enzyme (ACE)-inhibitors

Methanolic extracts, fractions and pure substances from *Musanga cecropioides*, *Cecropia species* and *Crataegus oxyacantha* were screened by using an *in vitro* bioassay based on the inhibition of ACE, as measured from the enzymatic cleavage of the chromophore-fluorophore-labelled substrate dansyltriglycine into dansylglycine and diglycine. At 0.33 mg/mL phenolic flavonoids and proanthocyanidins demonstrated inhibitory activity[31].

## 17. Immunomodulatory activity

Ethanol extract of *C. oxyacantha* helped alleviate pro-inflammatory immune responses associated with I/R-induced injury, boosted IL-10 levels, and increased Foxp3-positive T(regs) in the brain, which may have aided in suppression of activated inflammatory cells[38].

## 18. Dosage, toxicity, drug interactions

Hawthorn is a slow-acting herb and should be used for at least 4 to 8 weeks for full benefit. The dosage depends on the type of preparation and source material. Doses tested in



European clinical studies ranged from 160 to 900 mg a day of hawthorn extract, which is standardized to contain 2.2% of flavonoids or 18.75% of oligomeric proanthocyanidins. Within first two weeks of hawthorn supplementation positive effects will be observed. Hawthorn is safe and its side effects are minimal when consumed in recommended dosages<sup>[40]</sup>. No changes in blood status, liver enzymes, electrolytes, and glucose or erythrocyte sedimentation rate were observed in human clinical studies<sup>[41]</sup>. There are no adverse effects with low doses but higher doses increase the risk of drug induced hypotension and sedation. General symptoms of acute toxicity are bradycardia and respiratory depression leading to cardiac arrest and respiratory paralysis. The most frequent adverse events were dizziness, vertigo, gastrointestinal complaints, headache, nausea, migraine and palpitation<sup>[42]</sup>. It should not be used neither in children under 2 years of age<sup>[43]</sup> nor in pregnancy because of its demonstrable action on uterus (reduced tone and motility) *in vivo* and *in vitro*<sup>[44]</sup>. Hawthorn interactions are likely with agents that have effects 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. Use of hawthorn with  $\beta$ -blockers may bring about a mild rise in blood pressure in hypertensive patients, as  $\beta$ -blockers decrease cardiac output in such patients. However, no significant disease state interactions have been reported<sup>[45]</sup>.

## 19. Clinical trials

Meta-analysis randomized trial was conducted by Pittler *et al*<sup>[47]</sup> to assess the use of *C. oxyacantha* extract to treat patients with chronic heart failure. In most of the studies, Crataegus was used as an adjunct to traditional treatment, eight trials including 632 patients with chronic heart failure provided data that were suitable for meta-analysis. Symptoms such as dyspnea and fatigue improved significantly with hawthorn treatment as compared with placebo. In conclusion, these results suggest that there is a significant benefit from *C. oxyacantha* extract as an adjunctive treatment for chronic heart failure. Adverse effect relating to the use of *C. oxyacantha* preparations are infrequent and mild, even at higher dosage ranges but a retrospective study has suggested a negative results of the long term use of *C. oxyacantha* in the prognosis of heart failure<sup>[46]</sup>.

## 20. Conclusion

The ethnomedicinal and phytopharmacological data revealed the potential of various extracts from leaves, flowers, berries, bark of *C. oxyacantha* Linn. having cardioprotective, antioxidant, anti-inflammatory, gastroprotective, antimicrobial activities. The flavonoid components and oligomeric procyanidins present

in leaves, flowers and berries were responsible for Hawthorn pharmacological potential. Nevertheless further investigations are required to isolate pharmacologically active and industrially important phytoconstituents. This review also concludes that research on *C. oxyacantha* Linn. is carrying out in entire world including European, American, African, German, Asian countries.

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