

The genus *Crataegus*: chemical and pharmacological perspectives

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Abstract: Traditional drugs have become a subject of world importance, with both medicinal and economical implications. A regular and widespread use of herbs throughout the world has increased serious concerns over their quality, safety and efficacy. Thus, a proper scientific evidence or assessment has become the criteria for acceptance of traditional health claims. Plants of the genus *Crataegus*, Rosaceae, are widely distributed and have long been used in folk medicine for the treatment of various ailments such as heart (cardiovascular disorders), central nervous system, immune system, eyes, reproductive system, liver, kidney etc. It also exhibits wide range of cytotoxic, gastroprotective, anti-inflammatory, anti-HIV and antimicrobial activities. Phytochemicals like oligomeric procyanidins, flavonoids, triterpenes, polysaccharides, catecholamines have been identified in the genus and many of these have been evaluated for biological activities. This review presents comprehensive information on the chemistry and pharmacology of the genus together with the traditional uses of many of its plants. In addition, this review discusses the clinical trials and regulatory status of various *Crataegus* plants along with the scope for future research in this aspect.

Introduction

The genus name *Crataegus*, Rosaceae, is derived from a Greek word *kratos* meaning hardness of wood (Verma et al., 2007). *Crataegus* comprises of a complex group of trees and shrubs, native to Northern temperate zones, mostly between latitudes 30° and 50° N. *Crataegus* belongs to the subfamily Maloideae in the Rosaceae, a natural group of complex genera with the ability to interbreed freely (hybridize). They all possess the basal chromosome number of 17. In general they do not form large trees or exist as canopy dominants in forests. Some species are decidedly shrubby, whereas others can grow to heights of 12 m, although most species can attain tree-sized proportions. Hawthorn refers to the plant *Crataegus* and is widely distributed throughout the Northern temperate region of the world with approximately 280 species (Robertson, 1974; Huang et al., 2004; Donmez, 2004). *Crataegus* synonyms and common names in several European languages come from its physical characteristics of being a thorny bush, commonly used as hedging. The word 'haw' is an old English word for "hedge". The German *hagedorn*, meaning "hedgethorn", reveals that from a very early period, they were using *Crataegus* as hedging to divide their land into plots. The name

'may' is associated with the month in which the plant traditionally blossoms in England. Whitethorn *Crataegus* indicates the whiteness of its bark and the name 'Quickset' comes from its ability to establish itself rapidly. To appease their hunger before breakfast, farmers used to nibble on the flowers and leaves, hence the names Bread and Butter Tree or Bread and Cheese Tree.

General description

Leaves of the most species of *Crataegus* have two leafy bracts, their stalks meet the twig. Leaves are 15 mm-5 cm long, glabrous, broad-ovate or obovate and have toothed margins with three to seven lobes. The flowers grow in clusters of 5-12 with colour ranges from white to pink, pink to red. They contain both male and female sexes and are mostly fertilized by insects, which are attracted by the perfume released by the flowers. Red fruits are also known as Pixie Pears, Cuckoo's Beads and Chucky Cheese in some areas in England. These ovoid false fruits are known as Hawthorn berries which are greenish-red when they first appear, gradually turning bright red and then a deep red. They have meaty white flesh containing one or two stony fruits (WHO, 2003; Huang et al., 2004).



Review

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Distribution

These small sized trees are grown as a hedge plant in Europe. Found mostly in temperate areas including countries like North Africa, Western Asia, India, China and North America. In the 1800s, 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 *i.e.* tenacious and difficult to remove; it has been declared a noxious weed in many Australian states. In India, it is found in the temperate Himalayas, Kashmir and Himachal Pradesh, at an altitude of 1800-3000 m (Verma et al., 2007).

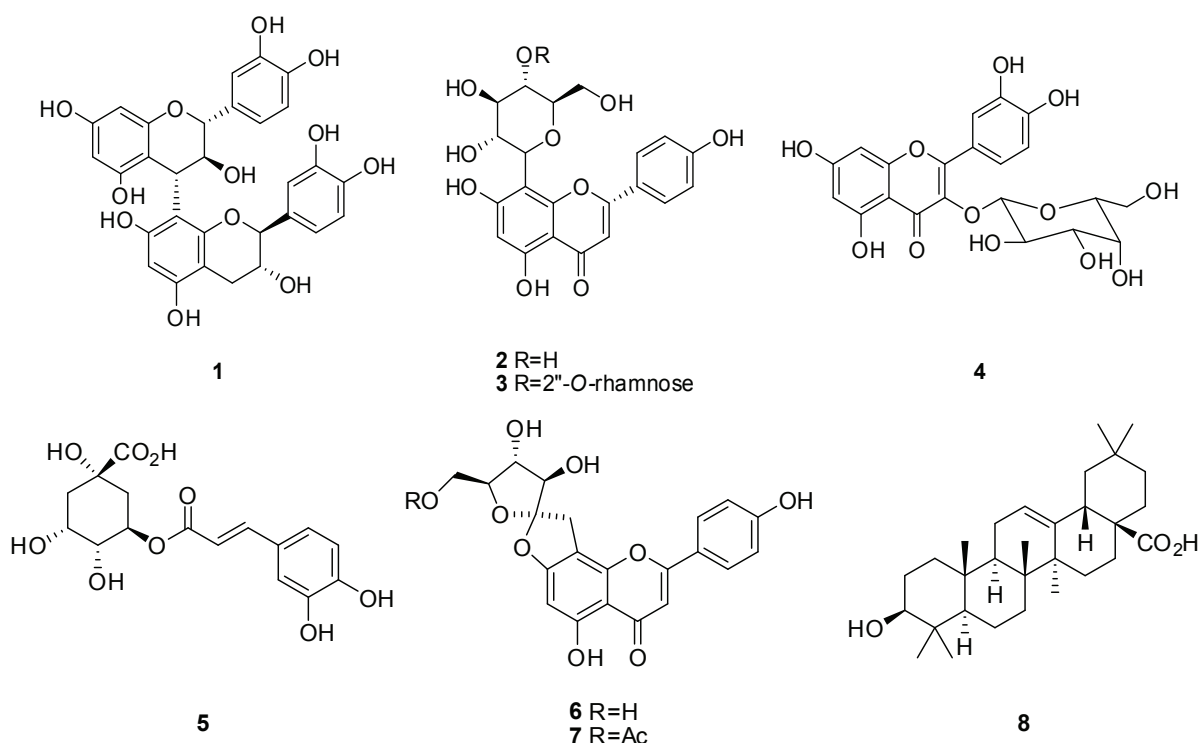
Traditional use

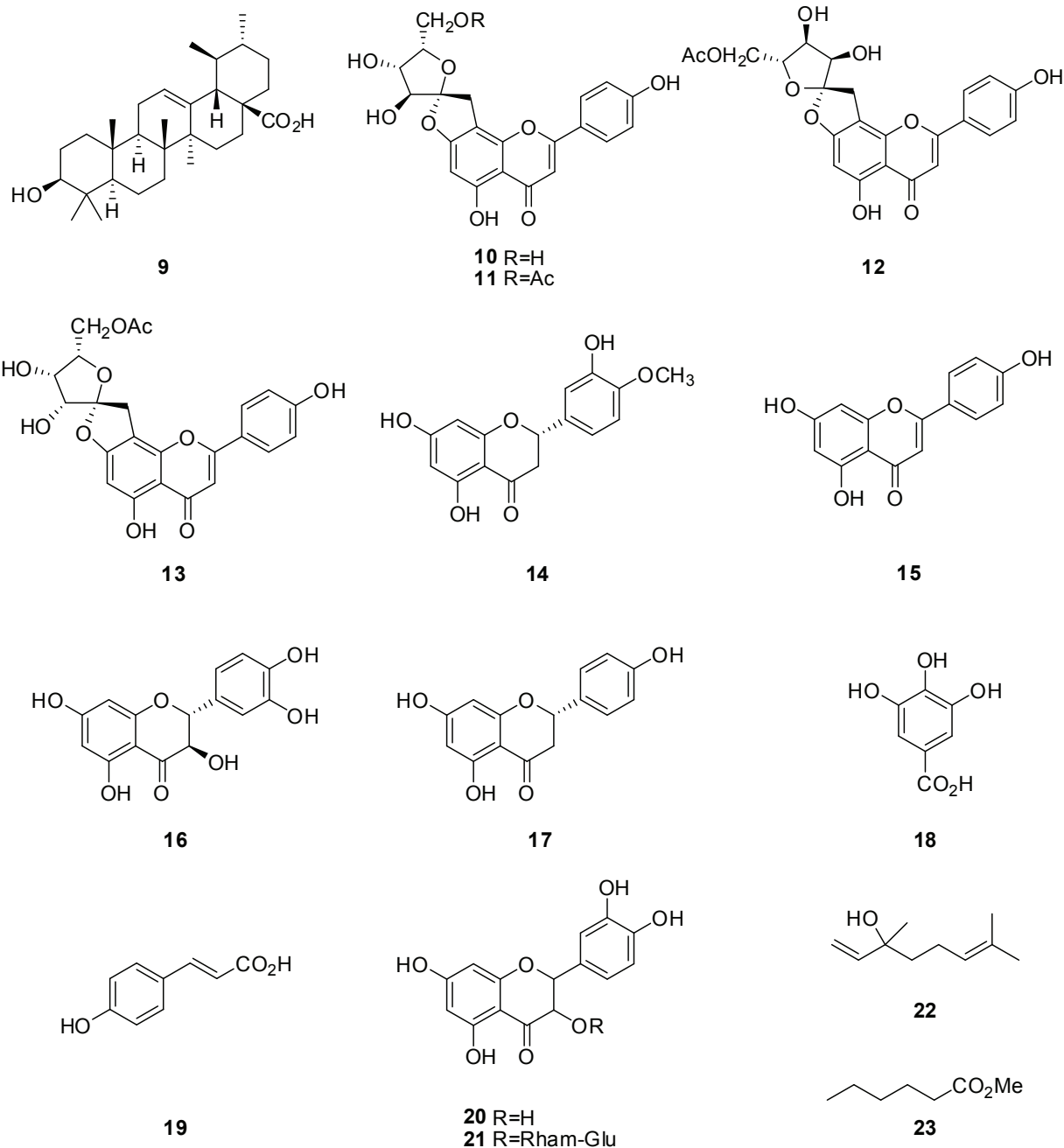
Crataegus species (hawthorn) have been used traditionally since ancient times. Furthermore, it has been proposed that its antioxidant constituents account for its beneficial therapeutic effects. A decoction of leaves and unripe fruits from *Crataegus aronia* is used to treat cardiovascular diseases, cancer, diabetes and sexual weakness in Arabian traditional medicine system (Miller, 1998; Ju, 2005). In Mexico, diabetes is treated with hawthorn extracts. Such treatment may be of considerable benefit especially during the early stages of the illness (Rigelsky & Sweet, 2002). In folk medicine, several hawthorn species are mainly used for treating cardiovascular diseases including *Crataegus*

pinnatifida (Chinese hawthorn), *C. pubesens* (Mexican hawthorn), *C. cuneata* (Japanese hawthorn), *C. laevigata* and *C. monogyna* (Europe), *C. oxycantha* and *C. aronica* (Middle East), *C. phaenopyrum* (American hawthorn) and *C. ambigua* (Russian hawthorn) (Khalil et al., 2008; Ljubuncic et al., 2005). Hawthorn (*C. pinnatifida*) is an edible fruit used in traditional Chinese medicine to lower plasma lipids (Lin et al., 2009). Dried fruits of *C. pinnatifida* have been used traditionally as oriental medicine and local soft drink material in Taiwan (Kao et al., 2007).

Chemistry

The leaves, flowers and berries of hawthorn contain a variety of bioflavonoid-like complexes that appear to be primarily responsible for the cardiac actions of the plant. Biflavonoids found in hawthorn plant include oligomeric procyanidins (OPC), vitexin, quercetin, and hyperoside. The action of these compounds on the cardiovascular system has led to the development of leaf and flower extracts, which are widely used in Europe. Other chemical constituents includes vitamin C, saponins, tannins, cardiogenic amines (phenylethylamine, tyramine, isobutylamine, *O*-methoxy phenylethylamine, choline and acetylcholine), purine derivatives (adenosine, adenine, guanine, caffeic acid, amygdalin), triterpene acids ursolic acid (Verma et al., 2007). Various reported chemical constituents from Genus *Crataegus* have been mentioned in Chart 1.





Pharmacological activities

Crataegus species possesses immense medicinal applications, but a few species have been screened for their biological activities. The experimental results have shown a wide spectrum of such effects; some of them have been discussed and summarized in Chart 2. *Crataegus* may improve coronary artery blood flow and the contractions of the heart muscle, hence used widely in cardiovascular disorders like arrhythmia, myocardial infarction, congestive heart failure (Long et al., 2006; Degenring et al., 2003; Tadic

et al., 2008; Jayalakshmi et al., 2006; Garjani et al., 2000). *Crataegus* extracts also prevents elimination of plasma lipids such as total cholesterol, triacylglycerides and LDL and VLDL fractions (Ljubuncic et al, 2006; Andrade-Cetto & Heinrich, 2005). *Crataegus* may be employed as anti-inflammatory, gastro-protective, antimicrobial agent and used as hepatoprotective agent (Tadic et al., 2008; Kao et al 2005). It is also mildly inhibits angiotensin converting enzyme (ACE) and reduce production of the potent blood vessel-constricting substance angiotensin II, hence act as hypotensive and diuretic (Schroder et al., 2003). It mildly

Chart 1. Bioactive compounds isolated from genus *Crataegus*.

Species	Chemical constituents	Compound name	References
<i>C. monogyna</i>	Phenolic compounds, di- <i>C</i> -glycosides	proanthocyanidin (1), vitexine-2- <i>O</i> -rhamnoside (3), hyperoside (4), anthocyanin, chlorogenic acid (5), epicatechin, apigenin-6,8-di- <i>C</i> -glycosides	Orhan et al., 2007; Bahorun, et al., 2003; Nikolov & Vodenicharov, 2003
<i>C. aronia</i>	Phenolics	oligomeric proanthocyanidin, flavanoids (vitexine-2- <i>O</i> -rhamnoside (3), hyperoside (4))	Orhan et al., 2007
<i>C. pseudoheterophylla</i>	Phenolics	oligomeric proanthocyanidin, flavanoids (vitexine-2- <i>O</i> -rhamnoside (3), hyperoside (4))	Orhan et al., 2007
<i>C. pinnatifida</i>	Flavanoid glycoside, furanoflavonoids, triterpenic acid, flavonoid ketohexosefuranosides, biphenyl glucoside	pinnatifin C (6), pinnatifin D (7), oleanolic acid (8), ursolic acid (9), pinnatifinoside A (10), pinnatifinoside B (11), pinnatifinoside C (12), pinnatifinoside D (13), shanyenoside A (5, 4'-dimethoxy-biphenyl-4-ol-3- <i>O</i> - β -D-glucoside)	Zhang et al., 2000; Maurya & Yadav, 2005; Lin et al., 2009; Chen et al., 2008; Zhang & Xu, 2001
<i>C. laevigata</i>	Oligomeric procyanidins	epicatechin-(4 β →8)-epicatechin-(4 β →6)-epicatechin, pentamer of (-)-epicatechin units linked through C-4 β /C-8 bonds	Svedstrom et al., 2002
<i>C. microphylla</i>	Flavanoids	hesperetin (14), apigenin (15), vitexin (2), vitexin-4'- <i>O</i> -rhamnoside	Melikoglu et al., 2004
<i>Crataegi folium</i>	Phenolics	catechin (16), naringenin (17), gallic acid (18), coumaric acid (19), caffeic acid	Demiray et al., 2009
<i>C. scabrifolia</i>	Carbohydrates	sugars, acids, sugar alcohols	Liu et al., 2010
<i>C. davisii</i>	Flavanoids	hyperoside (4), vitexin-2- <i>O</i> -rhamnoside (3), vitexin-4'- <i>O</i> -rhamnoside, rutin (20), quercetin (21)	Sozer et al., 2006
<i>C. macrocarpa</i>	Flavanoids	eriodictyol-7-glucuronide, luteolin-7- <i>O</i> -glucuronide	Ringl et al., 2007
<i>C. pentaegyna</i>	Phenolics	flavanoids	Ebrahimzadeh & Bahramian, 2009
<i>C. opaca</i> , <i>C. aestivalis</i> , <i>C. rufula</i>	Volatile components	linalool (22), hexanal, butyl hexanoate, pentyl hexanoate, methyl hexanoate (23)	Horvat & Chapman, 2007
<i>C. meyeri</i>	Carbohydrates	polysaccharides	Kuliev & Poletaeva, 1984
<i>C. curvisepala</i>	Flavanoids	cratenacin	Batyuk, 1996
<i>C. orientalis</i>	Carbohydrates	polysaccharides	Kuliev & Poletaeva, 1983
<i>C. turkestanica</i>	Phospholipids	phosphatidylethanolamine, phosphatidylcholine, phosphatidylinositol	Gazizov & Glushenkova 1996
<i>C. jackii</i> , <i>C. robesoniana</i> , <i>C. flabellata</i>	Essential oils	decane, linalool (22), syringaldehyde B, syringaldehyde C, syringaldehyde D, caryophylleneoxide, squalene, eicosane,	Kovaleva et al., 2009
<i>C. oxyacatha</i>	Flavanoids, Oligomeric procyanidins, Cardiotonic amines, triterpenes, Purine derivatives	heptahydroxyflavan glycoside, flavan polymers, quercetin (21), hyperoside (4), rutin (20), flavonoglycosyls, vitexin-4'-rhamnoside, epicatechol, tyramine, isobutylamine, <i>O</i> -methoxy phenylethylamine, ursolic acid (9), oleanolic acid (8), crategolic acid, adenosine, adenine, guanine, caffeic acid, polyphenols	Bersin et al., 1955; Rewerski & Lewak, 1967; Verma et al, 2007; Aneta & Oszmianski, 2007
<i>C. sanguine</i>	Flavanoid	acetylvitexin	Kashnikova et al., 1984; Kashnikova, 1984
<i>C. azarolus</i> var. <i>eu-azarolus</i> , <i>C. aronia</i>	Polyphenols	chlorogenic acid (5), hyperoside (4), quercetin (21), rutin (20), spiraeoside, epicatechin	Bahri-Sahloul et al., 2009
<i>C. sinaica</i>	Polyphenols	anthocyanin	Maharik et al., 2009
<i>Crataegi folium cum flore</i>	Flavanoids, flavone rotamers	flavonol 8-methoxykaempferol 3- <i>O</i> -(6"-malonyl-beta glucopyranoside	Amanzadeh et al., 2007; Rayyan et al, 2005
<i>C. cuneata</i>	Triterpenoid	cuneataol	Ikeda et al., 1999
<i>C. flava</i>	Eudesmanolide	1 β ,9 α -dihydroxyeudesm-3- <i>en</i> -5 β ,6 α ,7 α ,11 α H-12,6-olide	Ahmed et al., 2001

<i>C. macrocarpa</i>	Flavanoids	Vitexin (2), isovitexin, rutin (20), hyperoside (4), isoquercitrin (R)- and (S)-eriodictyol-7-O-β-D-glucuronide and luteolin-7-O-β-D-glucuronide	Ringl et al., 2007
<i>C. pubescens</i>	Polymer of sugar acids	pectinmethylesterase (PME)	Vivar-Vera et al., 2007
<i>C. maximowiczii</i>	Flavanoids	8-methoxykaempferol, vitexin (2), hyperoside (4), quercetin (21)	Bykov & Glyzin, 1972

lower blood pressure in some individuals with high blood pressure but should not be thought of as a substitute for cardiac medications for this condition. *Crataegus* showed high antioxidant and immunostimulating activity (Li et al., 2009). *Crataegus* is also employed in CNS disorders like anxiety and mild depression (Hanus et al., 2004).

Antihypertensive activity

It was observed that the hyperoside fraction and aqueous extract of *Crataegus tanacetifolia* prevented L-NAME-induced hypertension in rats and had beneficial effects on the cardiovascular system (Kocyildiz et al., 2006). In another study, the camphor-*crataegus* berry combination (CCC) drops decreased the orthostatic fall in blood pressure (Belz et al., 2002).

Anti-arrhythmic activity

Crataegus oxyacantha extract was compared with other known cardioactive drug like ouabain, epinephrine, milrinone and propranolol for anti-arrhythmic potential. Extract showed a unique activity profile as compared to conventional cardiac drugs. Its extract appeared to be capable of inducing rhythmicity in quiescent cardiomyocytes and showed antiarrhythmic activity. The commercial hawthorn preparations also exhibit similar chronotropic activities. Its extract also showed negative chronotropic effects and does not cause β-adrenergic receptor blockade (Long et al., 2006).

Myocardial infarction

Crataegus extract (hawthorn) possess positive inotropic effect of amines such as phenethylamine, *O*-methoxyphenethylamine and tyramine. These amines were responsible for *in vitro* activity of *Crataegus* extracts on the guinea pig papillary muscle (Wagner & Grevel, 1982) and it also raised intracellular calcium thus prolongs the action potential, which supports for its inotropic activity (Kocyildiz et al., 2006). In another study, alcoholic extract of *Crataegus oxyacantha* (AEC) was found to maintain mitochondrial antioxidant status, decreased Krebs cycle enzymes induced by isoproterenol in rat heart and prevented mitochondrial lipid peroxidative damage (Jayalakshmi et al., 2006).

Myocardial ischaemia

Hawthorn used as anti-atheromatous and coronarodilatating agent (Petkov, 1979). The hydroalcoholic extract of *Crataegus meyeri* (1 mg/kg/min) infused to rats, resulted in a significant decrease in the total number of ventricular ectopic beats. Chloroform extract of *Crataegus meyeri* (1 mg/kg/min) infused also reduced the total number of ventricular ectopic beats but this reduction was due to the decrease of single extra systoles. Hydroalcoholic and ethyl acetate infused extracts significantly reduced the time spent for ventricular fibrillation. During the extract infusion there were no significant changes in the heart rate and blood pressure but bolus injection of all the extracts significantly reduced the blood pressure. Thus, the extracts of *Crataegus meyeri* may possess active principles which have a hypotensive and antiarrhythmic potential on ischaemic myocardium (Garjani et al., 2000). In another study *Crataegus oxyacantha* extract was evaluated to prevent ischemia-reperfusion injury in an *in vivo* rat model of acute myocardial infarction. *Crataegus* extract (100 mg/kg body weight) showed a significant decrease in creatine kinase activity and infarct size. At the molecular level, *Crataegus* administration resulted in a significant attenuation of phosphatase and tensin homolog, deleted on chromosome, up regulation of phospho-Akt and c-Raf levels in the heart and this suggested that *Crataegus* extract attenuated apoptotic incidence in the experimental myocardial ischemia-reperfusion model by regulating Akt and hypoxia-inducible factor (HIF-1) signalling pathways (Garjani et al., 2000).

Congestive heart failure

Crataegus is used widely in cardiology (Blesken, 1992). The standardised extract of fresh berries of *Crataegus oxyacantha* L. and *C. monogyna* Jacq. (Crataegisan®) have shown potent effect in patients with cardiac failure NYHA class II. A total of 143 patients were treated with three times 30 drops of the extract or placebo orally administered for eight weeks. The results showed a significant improvement in their heart failure condition under long term therapy with the standardised extract of fresh *Crataegus* berries (Degenring et al., 2003). In another study, the *Crataegus* extract WS 1442 inhibited balloon catheter-induced intimal hyperplasia in the rat carotid artery by directly influencing platelet-derived growth factor receptor (PDGFR-beta). The results indicated that the polyphenols might be responsible

Chart 2. Pharmacological activities of *Crataegus* species.

Species	Part/extract	Pharmacological activities	References
<i>C. oxyacantha</i>	Leaves, stem, dried berries (alcoholic)	Negative chronotropic effect, cardiogenic, congestive heart failure treatment; free-radical-scavenging, anti-inflammatory, gastroprotective and antimicrobial activities; myocardial infarction treatment, antioxidant, inhibition of thromboxane A ₂	Long et al., 2006; Degenring et al., 2003; Tadic et al. 2008; Jayalakshmi et al., 2006; Anna et al., 2007
<i>C. aronia</i>	Berries, leaves, flowers (aqueous)	Antioxidant; antidiabetic	Ljubuncic et al. 2005; Ljubuncic et al., 2006
<i>C. laevigata</i>	Berries (dichloromethane and methanol)	Antioxidant	Kirakosyan et al., 2003
<i>C. monogyna</i>	Flowers bearing branches, fruits (dichloromethane, ethanol)	Antioxidant, negative chronotropic effect	Kirakosyan et al., 2003; Degenring et al., 2003
<i>C. pinnatifida</i>	Berries, fruits, leaves (dichloromethane, ethylacetate, acetone, ethanol, heptane, hot water)	Lipid-lowering, anti-inflammatory, against oxidative stress, anticataract potential, immunobiological; hepatoprotective, cytotoxic	Lin et al., 2009; Wang et al., 2011; Li et al., 2009; Kao et al., 2005
<i>C. meyeri</i>	Flower heads (petroleum ether)	Myocardial ischaemia	Garjani et al., 2000
<i>Crataegi folium</i>	Leaves (acetone, methanol, water)	Antioxidant	Demiray et al., 2009
<i>C. mexicana</i>	Root infusion; leaves (hexane)	Hypoglycaemic. relaxant effect on guinea pig tracheal smooth muscle	Andrade-Cetto & Heinrich, 2005; Arrieta et al., 2010
<i>C. aronia, C. monogyna, C. pseudoheterophylla</i>	Leaves, fruits (ethanolic)	Antibacterial, antifungal, antiviral, antidiabetic	Orhan, et al., 2007
<i>C. tanacetifolia</i>	Leaves (water)	Hypotensive, antimicrobial	Kocylidiz et al., 2006
<i>C. pentaegyna</i>	Fruits (methanolic, aqueous)	Antioxidant	Ebrahimzadeh & Bahramian, 2009
<i>C. microphylla</i>	Fruits (methanolic)	Radioprotective	Hosseini-mehr et al., 2009.
<i>C. sinaica</i>	Fruits, leaves (acetone, ethyl acetate, butanol, water)	Antiviral, including anti-HIV, antioxidant, anti-complementary	Shahat et al., 1996; Shahat et al., 1998
<i>Crataegus</i> spp.	Fruits, leaves	Diuretic/ACE inhibitor	Schroder et al., 2003
<i>C. azarolus</i> var. eu- <i>azarolus</i>	Flower (ethyl acetate)	Antioxidant, treatment of ischaemic heart failure	Bahri-Sahloul et al., 2009;
<i>C. bornmulleri</i>	Fruits (ethyl acetate)	Antimicrobial	Guyen et al., 2006.
<i>C. cuneata</i>	Roots (water decoction)	Improve sperm motility	Hu & Xiong 2006.
<i>C. orientalis</i>	Leaves (ethanolic)	Antithrombotic	Arslan et al., 2010.

to ameliorate post-angioplasty restenosis and prevent balloon catheter-induced intimal hyperplasia (Furst et al., 2010).

Antihyperlipidemic activity

Crataegus pinnatifida is an edible fruit used in traditional Chinese medicine to lower plasma lipids. A study was conducted on hawthorn fruits for investigation of its lipid-lowering property. Hawthorn powder extracts inhibited acylCoA: cholesterol acyltransferase (ACAT) activity in Caco-2 cells. The triterpenic acids like oleanolic acid and ursolic acid in the extracts were responsible for its cholesterol lowering effects and it was also found that plant sterol esters provide an additive effect in combination to triterpenic acids (Lin et al., 2009). In another study aqueous extract of *Crataegus*

aronica fruits exerted hypolipidaemic potential which was determined on rabbits fed with an atherogenic diet. Hawthorn fed rabbits showed inhibition of intestinal acylCoA: cholesterol acyltransferase without effecting the activities of hepatic 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMG-CoA-R) or cholesterol 7 α -hydroxylase which explain its hypolipidaemic potential (Khalil et al., 2008).

Antioxidant activity

Crataegus laevigata and *C. monogyna* (hawthorn) were subjected to drought and cold stress treatments, and such treatments caused enhanced the antioxidant capacity of the extracts (Kirakosyan et al., 2003) In another study, aqueous extract of leaves and unripe fruits of *Crataegus aronia* was investigated

for its antioxidant potential which were found to be significant (Ljubuncic et al., 2005). Other species of *Crataegus* exhibiting antioxidant activity includes *C. pentaegyna* (Ebrahimzadeh & Bahramian, 2009), *C. folium* {Hawthorn} (Demiray et al., 2009).

Anticataract potential

Cataract is a multifactorial disease primarily associated with oxidative stress produced by free radicals and is the leading cause of blindness worldwide. Both *in vitro* and *in vivo* studies were undertaken to investigate the anticataract potential of *Crataegus pinnatifida* leaves extract. *In vitro* antioxidant assay of *Crataegus pinnatifida* leaves extract on NO (nitric oxide) production inhibition, aldose reductase inhibition, and O₂⁻ radical scavenging activities reveals its potential of antioxidant. The *in vivo* screening investigation of *C. pinnatifida* leaves extract eye drops in 0.1% hydroxypropyl methyl cellulose solution were prepared to evaluate the anticataract potential. Administration of leaves extract eye drops alternately three times a day in rat pupils with selenite-induced oxidative stress significantly increased serum superoxide dismutase (SOD) and catalase (CAT) activities and tended to reduce malondialdehyde (MDA) level compared with control group. The antioxidant enzymes SOD, CAT, and GSH (glutathione) activities in lens showed a significant increase, thus explains its antioxidant as well as anticataract potential (Wang et al., 2011).

Anti-inflammatory, gastroprotective and antimicrobial activity

Crataegus monogyna, *C. oxycantha* and *C. laevigata* were shown anti-inflammatory, gastroprotective and antimicrobial activities. Oral administration of extract caused dose-dependent effect in a model of carrageenan-induced rat paw edema and showed anti-inflammatory activity. Extract also produced dose-dependent gastroprotective activity in ethanol-induced acute stress ulcer in rat model. 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*, *Lysteria monocytogenes* and *Candida albicans* (Tadic et al., 2008). *Crataegus tanacetifolia* (Lam.) extract had bactericidal effects (Benli et al., 2008).

Antiviral activity

This activity was investigated on leaves and berries of three *Crataegus* species including *C. aronia* var. *aronia*, *C. monogyna* as well as *C. pseudoheterophylla* and was also evaluated for flavonoid amount and total proanthocyanidin content. Results revealed that the

extracts containing these active constituents have been verified to be highly effective against Herpes simplex virus (Orhan et al., 2007).

The flavonoids and trimeric procyanidin isolated from *Crataegus sinaica* demonstrated antiviral activity against HIV. Hyperoside, vitexin, 2''-O-rhamnosylvitexin, (4'''-O-acetyl)-2''-O-rhamnosylvitexin, epicatechin, (+)-taxifolin, 3-O-β-xylopyranosyl-(+)-taxifolin may exert their antiviral effects by binding to the protein coat of the virus itself or by inhibiting reverse transcriptase in retroviruses like HIV (Shahat et al., 1998).

Crataegus on reproductive system

Crataegus cuneata effect on reproductive system was evaluated using medicated serum prepared from its root part. This serum can improve *in vitro* sperm motility of asthenospermia patients. The sperm specimens of sixteen asthenospermia patients were co-incubated with the medicated serum *in vitro* and sperm motility characteristics were evaluated by computer-assisted semen analysis. When compared with the control group, the medicated serum significantly increased the sperm progressive motility in 5 and 15 min and the motility and progressive motility were both increased significantly in 60 and 120 min (Hu & Xiong, 2006).

Radioprotective activity

The fruit of *Crataegus microphylla* extract when administered intraperitoneally at doses of 25, 50, 100 and 200 mg/kg, 1 h prior to gamma radiation, reduced the frequencies of micro nucleated polychromatic erythrocytes (MnPCE). All four doses of hawthorn extracts significantly reduced the frequencies of MnPCE and increased the PCE/PCE+NC ratio (polychromatic erythrocytes/polychromatic erythrocytes+normochromatic erythrocytes) in mice bone marrow cells compared with the non drug treated irradiated control group. It appeared that hawthorn extract exhibits antioxidant activity and reduced the genotoxicity induced by gamma radiation in mouse bone marrow cells. Phytochemical study revealed that *C. microphylla* contains high amounts of phenolic compounds, chlorogenic acid, hyperoside and epicatechin which might be responsible for its radioprotective potential (Hosseinimehr et al., 2007).

Immunostimulant activity

Water-soluble polysaccharide from *Crataegus pinnatifida* Bge. exhibits immunostimulant activity. Two sub-fractions of this polysaccharide fraction were evaluated on the basis of phagocytosis of macrophage assay, natural killer cells cytotoxicity and spleen lymphocyte proliferation assays. The results showed that

these polysaccharides significantly induced phagocytic rates and phagocytic indexes by peritoneal macrophages and thus suggested that they should be explored as a novel potential immunostimulants from *Crataegus* (Li et al., 2009).

Crataegus in anxiety and depression

A large randomized controlled trial (RCT) found that a combination of *Crataegus oxyacantha* (hawthorn), *Eschscholzia californica* (Californian poppy) and magnesium was more effective than placebo in reducing anxiety in 264 individuals with generalised anxiety disorder (Hanus et al., 2004). Another study evaluated for the central effects of the phytotherapeutic product-CPV (dry extract of *Crataegus 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. CPV extract (430 and 860 mg/kg) presented an anxiolytic effect on rats (increased the number of entries into the open arms in the EPM) and, furthermore, a tendency of slight amnesic effect for the doses (430 and 860 mg/kg), but less intense when compared to diazepam (1.5 mg/kg), (Min et al., 2000; Tabach et al., 2009).

Diuretic/ACE inhibitor activity

A study had been done to check this activity experimentally which involves the use of a homeopathic *Crataegus* preparation Cralonin. In this study the efficacy of the homeopathic *Crataegus* preparation for non-inferiority to standard treatment for mild cardiac insufficiency was compared. Multicentre non-randomised cohort study was conducted in patients aged 50-75 years in New York Heart Association class II. Patients received Cralonin (*ns*110) or ACE inhibitor diuretics (*ns*102) for eight weeks. To adjust for confounding by baseline factors, populations were stratified according to propensity score. After adjusting, there were no statistically significant differences between treatment groups. The *Crataegus*-based preparation Cralonin is non-inferior to usual ACE inhibitor diuretics treatment for mild cardiac insufficiency on all parameters except BP reduction (Schroder et al., 2003).

Hypoglycaemic activity

Diabetes mellitus is a syndrome which affects more and more people in all countries over the world. *Crataegus* containing herbal extracts were used widely to treat this condition in Mexico. Such treatment may be of considerable benefit especially during the early stages of the illness. *Crataegus mexicana* Moc., *C. pubescens*, and *C. presl* root infusion containing active constituents like

tannins and flavonoids may act as antidiabetic (Andrade-Cetto & Heinrich, 2005). In another study the effects of a decoction prepared from the leaves and unripe fruits of *Crataegus aronia*, in streptozotocin-induced diabetic rats, were conducted and its effect on plasma and tissue indices of oxidative stress, as well as blood glucose levels was measured. This study concluded that decoction prepared from the leaves and unripe fruits of *C. aronia* normalizes plasma lipid peroxide levels and lowers blood glucose levels in diabetic (Ljubuncic et al., 2006).

Hepatoprotective activity

Crataegus pinnatifida was investigated for hepatoprotective activity and the results suggested that this plant has anti-inflammatory potential which play a role in hepatoprotection (Kao et al., 2005).

Cytotoxic activity

Cytotoxic ursane-type triterpenes were isolated from *Crataegus pinnatifida* which were identified as uvaol, ursolic acid and 3-oxo-ursolic acid. The cytotoxic activities of these compounds were tested *in vitro* against murine L1210 and human cancer cell lines (A549, SK-OV-3, SK-MEL-2, XF498, and HCT15). Uvaol and ursolic acid showed moderate cytotoxicities against L1210, whereas they showed weak activities against human cancer cell lines. However, 3-oxo-ursolic acid exhibited potent cytotoxic activities both in murine and in human cancer cell lines (Min et al., 2000). Another study to clarify the active components in anti-transformation and anti-tumor promotion, involved the collection of the polyphenol fraction (CF-TP) of hot-water extracts from dried fruits of *C. pinnatifida* and different assays were conducted using this fraction such as anchorage-independent transformation assay. CF-TP significantly inhibited 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced cell transformation in JB6 P⁺ cells. The results indicated that CF-TP significantly inhibited the generation of reactive oxygen species (ROS) and the phenomena of inflammation induced by TPA. It also suppressed the expression of COX-2 and iNOS, and the activation of ornithine decarboxylase (ODC). Furthermore, CF-TP inhibited benzo[α]pyrene (B[α]P)/TPA-induced skin tumor formation and decreased the incidence of tumor. The results revealed that CF-TP possesses potential as a cancer chemopreventive agent against tumor promotion (Kao et al., 2007).

Miscellaneous

Crataegus species have number of various biological as well as pharmacological activities as shown in Table 1.

Dosage

Dosages of *Crataegus* extracts vary, depending upon concentration of extract. Therapeutic dose of an extract standardized to contain 1.8 percent vitexin-4-rhamnoside is 100-250 mg three times daily. A standardized extract containing 18% oligomeric procyanidins is dosed in the range of 250-500 mg daily (Monograph, 2010).

Toxicology

Crataegus has been shown to have low toxicity with an LD50 of 25 mg/kg (Ammon & Handel, 1981a). Commission E monograph states that mice and rats have been safely given a standardized extract at doses up to 3 g/kg body weight (Blumenthal et al., 1988). Studies in rats using excessive dosing of hawthorn flower extract (600 mg/kg/day; flavonoids) over 30 days showed unremarkable adverse events. In humans the acute oral toxicity of hawthorn was 6 g/kg.

Contraindications

It is generally considered safe; however relative contraindications exist with cases of hypersensitivity or a history of an allergic reaction to *Crataegus* or any of its components. An absolute contraindication has been suggested in children under the age of 12 (Weikl et al., 1996; Ammon & Handel, 1981b).

Side effects

Hawthorn was well tolerated in studies lasting up to sixteen weeks. Some side effects, while rare, may have been related to hawthorn extracts cited in the literature are: mild rash, headache, sweating, dizziness, sleepiness, agitation, gastrointestinal complaints (Houser, 2006).

Drug interactions

The flavonoid components of hawthorn may be responsible for hawthorn's beneficial effects in the treatment of heart failure. However, these components may also affect P-glycoprotein function and cause interactions with drugs that are P-glycoprotein substrates, such as digoxin, which is also used to treat heart failure (Tankanow et al., 2003).

Preparations

Tincture, decoction and powder.

Products

Tincture, capsule, tablet, bulk herb and syrup

(Tankanow et al., 2003).

Clinical trials of hawthorn (*Crataegus*)

Clinical trials are a means of developing new treatments and medications for diseases and conditions. Clinical trials are conducted to allow safety and efficacy data to be collected for health interventions (e.g., drugs, diagnostics, devices, therapy protocols). Clinical trial reviewed in this paper have been inconsistent in terms of criteria used (sample size, preparation and dosage, trial period, assessment method) but have been largely consistent with regards to positive outcome results. Adverse effect relating to the use of hawthorn 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 hawthorn in the prognosis of heart failure (Tassell et al., 2010; Zick et al., 2008). Clinical studies on hawthorn (*Crataegus*) preparations have been shown in Table 3.

Regulatory status for hawthorn in selected countries

Regulatory Affairs, also called Government Affairs, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory Affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, Biologics and functional foods) (Houser, 2006) Chart 3.

Worldwide used species of *Crataegus* as herbal drug or drug material

More than twenty species of hawthorn are used as herbal drugs or drug materials in the world. Some of them are officially listed in the pharmacopoeias of many countries such as China, Germany, France and England (Chang et al., 2002) Chart 4.

Conclusion

The medicinal properties of *Crataegus* species, Rosaceae, as discussed in this review paper highlighted significant pharmacological activities of this species. Pharmacological actions experimented on animals or *in vitro* models conclude its potential as cardioactive, hypotensive, hypolipidaemic, gastroprotective, hepatoprotective, antiviral, including anti-hiv, antioxidant, immunostimulant, antidiabetic, cytotoxic etc. Presence of bioflavonoids like oligomeric procyanidins, triterpenes, polysaccharides and other active compounds might be responsible for these pharmacological activities. It is believed that detailed information as presented in this review on its various biological properties, chemistry

Table 1. Clinical Studies on Hawthorn (*Crataegus*) Preparations.

Nature of trial	Patient type	Hawthorn preparation and Dosage	Number of patients	Trial length in weeks	Assessment method	Results for hawthorn group	Reference
Randomized, placebo controlled double blind	New York Heart Association (NYHA) stage II heart failure	Hawthorn extract 180mg	80	6	Bicycle ergometry exercise	A statistically significant improvement in general well-being, cardiac function, dyspnea, palpitation. Slight but significant improvement in lowering blood pressure. No differences were noted in improvement of the ECG compared with control group.	Iwamoto et al., 1981
Open trial	Hypertlipidemic	Hawthorn (shan zha) drink 250 mL drink (0.56 mg flavones/100 mL) bid	30	4.3	Serum lipid analysis	Significantly decreased serum cholesterol ($p < 0.001$), LDL-C, and triglyceride compared with that before treatment. Significant malondialdehyd reduction showed strong antioxidant effect	Chen et al., 1995
Randomized, placebo controlled double blind	New York Heart Association (NYHA) stage II heart failure	WS1442 (80 mg)	136	8	Bicycle ergometry exercise	Significant advantage in postexercise pressure/heart rate product, heart rate, and subjective patient symptomatology.	Weikl et al., 1996
Randomized, placebo controlled double blind	New York Heart Association (NYHA) stage II heart failure	WS1442 (240 mg)	40	12	Exercise tolerance	Improved oxygen utilization efficiency of myocardial muscle	Zapfe, 2001
Randomized, placebo controlled double blind, multicentre trial	Chronic congestive heart failure (NYHA stage III)	WS1442 (1800 mg)	209	16	Bicycle ergometry exercise	Dose-dependent effect of WS 1442 on the exercise capacity of patients with heart failure and on typical heart failure-related clinical signs and symptoms. The drug was shown to be well tolerated and safe.	Tauchert, 2002
Multicentre, nonrandomized cohort study	New York Heart Association (NYHA) stage II heart failure	Cralonin (homeopathic preparation), 20 Drops tds	212	8	Walk test, staircase test, nocturnal, urination	Cralonin is non-inferior to usual ACE inhibitory diuretics treatment for mild cardiac insufficiency on all parameters except BP reduction.	Schroder et al., 2003
Double-blind, randomised, placebo-controlled	Mild-to-moderate anxiety patients	Combined plant extracts of <i>Crataegus oxyacantha</i> and <i>Eschscholtzia californica</i>	264	12	Total Hamilton anxiety scale	The preparation containing fixed quantities of <i>Crataegus oxyacantha</i> , <i>Eschscholtzia californica</i> , and magnesium proved safe and more effective than placebo in treating mild-to-moderate anxiety disorders.	Hanus et al., 2004
Randomized, placebo controlled double blind	Type 2 diabetics and hypertensive patients	<i>Hawthorn extract 1200 mg</i>	80	16	Blood pressure, glycaemic control	<i>Crataegus laevigata</i> cause reduction in diastolic blood pressure in participants with type 2 diabetes taking prescribed medication. This study also showed no herb-drug interactions arising from hawthorn administration.	Walker et al., 2006
Retrospective analysis on data obtained from the HERB (H Extract Randomized Blinded chronic HF Study).	New York Heart Association (NYHA) stage II-IV heart failure	WS1442 900 mg	120	6	Walking exercise	<i>Crataegus oxyacantha</i> Special extract WS 1442 does not reduce heart failure progression in patients who have mild to moderate HF. <i>Crataegus</i> Special Extract WS 1442 appears to increase the early risk of heart failure progression.	Zick et al., 2008
Double-blind, randomised, placebo-controlled	New York Heart Association (NYHA) stage II –III heart failure	WS1442 450 mg	120	24	Maximal treadmill exercise testing	Hawthorn provides no symptomatic or functional benefit when given with standard medical therapy to patients with heart failure.	Zick et al., 2009

Chart 3. Regulatory status of *Crataegus*.

Country name	Regulatory status
Australia	Hawthorn is not included in Part 4 of Schedule 4 of the <i>Therapeutic Goods Regulation</i> .
US	Hawthorn flower and leaf is official in <i>United States Pharmacopeia. National Formulary</i> (USP26. NF 21, 2003). Hawthorn does not have generally recognised as safe (GRAS) status, however it is freely available as dietary supplement in the US under DSHEA legislation (Dietary Supplement Health and Education Act of 1994).
UK and Germany	Hawthorn berry, flower and leaf are each individually covered by a negative assessment. Hawthorn is not included in General Sale List. Hawthorn leaf and flower combined are covered by a positive Commission E Monograph. Hawthorn berries and hawthorn leaf and flower are official in <i>European Pharmacopeia</i> 4.3.

Chart 4. Worldwide acceptance of *Crataegus* species.

Pharmacopoeias	Species accepted	Parts used
British Pharmacopoeia (2000)	<i>C. oxyacantha</i> L., <i>C. monogyna</i> Jacq.	Fruits, leaves, and flowers
European Pharmacopoeia (1998)	<i>C. oxyacantha</i> L., <i>C. monogyna</i> Jacq.	Fruits, flowers
Chinese Pharmacopoeia (English ed., 1997)	<i>C. pinnatifida</i> Bge., <i>C. pinnatifida</i> Bge. var. <i>major</i> N.E. Br.	Fruits
France Pharmacopoeia (1998)	<i>C. oxyacantha</i> L., <i>C. monogyna</i> Jacq.	Fruits
German Pharmacopoeia (DAB, 1997) and Swiss Pharmacopoeia (1997)	<i>C. oxyacantha</i> L., <i>C. monogyna</i> Jacq., <i>C. pentagyna</i> Waldst. C. <i>nigra</i> Waldst., <i>C. azarolus</i> L.	Leaves with flowers

of compounds, clinical trials and regulatory status of *Crataegus* might provide incentive for proper evaluation of the use of its various species in medicine. Last but not the least, this review emphasizes the potential genus *Crataegus* to be employed in new therapeutic drugs and provide the basis for future research on the various species of this genus.

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