International Journal of Multidisciplinary Research and Development
Online ISSN: 2349-4182, Print ISSN: 2349-5979; Impact Factor: RJIF 5.72
www.allsubjectjournal.com
Volume 3; Issue 4; April 2016; Page No. 73-76

Pharmacological activities of *Crataegus* species: A review

[1] Jibrin Bala Yusuf, [2] Ali H Meriçli

Department of Pharmacognosy, Near East University, Nicosia via Mersin-10, P.O. 99138, Cyprus

Abstract
The importance of plants in the management of diseases, as well as provision of raw materials for the pharmaceutical industries could not be over emphasized. *Crataegus* species are part of the important plant family Rosaceae. Members of the genus have been popular for their long term history of use in the treatment and control of metabolic as well as endocrine diseases that are detrimental to human health. It is because of their widely reported folkloric and pharmacological activities that this review was conducted, in order to have a compilation of the activities of some of the investigated members of the genus. Google scholar, Science direct, WEBMD, Drugs.com, among other sources, were visited in obtain first hand and genuine information on the pharmacological activities of the plants. Due to extensive research on some particular as well as most popular plants of the genus, the number of plants covered by this review stood at seven (7), though with so many therapeutic potentials such as antidiabetic, anti-inflammatory, antihyperlipidemic, and cardiovascular activities, to mention but a few.

Keywords: *Crataegus* species, medicinal plants, flavonoids, cardiovascular diseases

1. Introduction
Since time immemorial, plants have been used as sources of food and medicine. As cited in Yusuf JB, it is estimated that the number of medicinal plants in the world lies in the range of 30,000 to 75,000 [3]. A WHO study shows that 80% of the inhabitants of the world solely depend on medicinal plants for the prevention, treatment, and/or cure of diseases [48]. *Crataegus* species are sources of numerous bioactive compounds with therapeutic as well as pharmaceutical importance. For example, the Chinese hawthorn (*C. pinnatifida* Bunge.) alone was reported to contain more than 150 different compounds including, but not limited to flavonoids, lignans, hydroxycinnamic acids, monoterpenoids, sesquiterpenoids, steroids, and triterpenoids [21] . *Crataegus* is one of the more than 90 genera of the family Rosaceae (global.britannica.com,). The genera consists of 1478 plants, out of which 64 species are accepted, and 245 are of infraspecific rank (www.theplantlist.org/browse/A/Rosaceae/Crataegus), with *Crataegus* alone consisting of approximately 300 species [28]. *C. oxyacantha* L. (syn. *C. laevigata* Poir) and *C. monogyna* Jacq. are the species that are commonly useful in commercial preparations. *Crataegus oxyacantha* L. is also known as haw, maybush, or whitehorn, and is native to temperate regions in the Northern Hemisphere of Asia, Europe, and North America [8]. *Crataegus monogyna* Jacq. and *Crataegus laevigata* Poir. are the major hawthorn species found in middle Europe, *C. pentagyna* Waldst.&Kit., *C. nigra* Waldst.&Kit., and *C. azarolus* L. in southern and southeastern Europe, while *C. pinnatifida* Bunge. and *C. scabrifolia* (Franchet) Rehder. are the dominant species in China [35, 47]

In folk medicine, among other uses, hawthorn has been used for the treatment of diarrhea, gall bladder disease, insomnia, and also in the treatment of asthma (as an antispasmodic agent) [13]. The Chinese use it for a variety of conditions such as digestive problems, dyspnea, hyperlipidemia, and poor circulation [1, 37]. In Isreal and neighboring Arab countries, *C. aronia* (L.) DC. has been used for the treatment of cancer, diabetes, and sexual weakness [26]. For example, traditionally, the Natives of China use the dried berries as digestive aid; and are often made into candies, jam, jelly, or wine [33]. They may also be available as authorized prescription drugs, over-the-counter (OTC) medications, authorized phytomedicines, as supplements, or as unregulated herbal remedies, as mainly found in developing countries. A meta-analysis of randomized, placebo-controlled trials of hawthorn extract in combination with standard congestive heart failure (CHF) therapy suggested several beneficial cardiovascular effects of hawthorn as compared to placebo [34]. Currently, scientists claimed that hawthorn could be used as an alternative therapy for the treatment and prevention of cardiovascular diseases such as angina, arrhythmia, hyperlipidemia, hypertension, and New York Heart Association (NYHA) functional class II congestive heart failure [5, 29].

1.1 Drug forms
Berries (unripe fruits), flowers, leaves, and stem bark are the most utilized parts of *Crataegus*. The drugs are subjected to methanol, ethanol, or water-based extraction to obtain the extract that could be used in the formulation of the desired preparation(s) [19]. Products from crataegus species could be in the form of tinctures, tablets, teas, and aqueous extracts [16, 20]

1.2 Constituents of *Crataegus*
Flavonoids and oligomeric proanthocyanidins are mainly responsible for the pharmacological and bioactivities of *Crataegus* [31]. Blumenthal M. reported the presence of Quercetin-3Dgalattoside, vitexin-2-O-rhamnoside, and acetylvitexin-2-O-rhamnoside as the main glycosides found in different parts of *Crataegus* [2]. Vitexin, hyperoside, rutin, and catechin derived oligomeric procyanidins (OPC) have also been reported to be among the most important constituents. Triterpenic acids (ursolic, oleanolic, and crataegolic acids) and

phenol carboxylic acids (chlorogenic and caffeic acids and various amines) have also been isolated, and are thoroughly investigated in in vitro experiments in animal studies, and in human clinical trials [11, 30, 36, 43]. Currently, the most studied hawthorn extracts are WS 1442 (a standardized dry 45% ethanol extract adjusted to a content of 18.75% OPC with a starting plant material/extract ratio of 4 to 7:1), and LI 132 (70% methanol extract adapted to a content of 2.2% flavonoids) [12, 14, 23].

2. Pharmacological activities of *Crataegus*

2.1 Management of cardiovascular diseases

Predominantly, monopreparations are best for the treatment of congestive heart failure. *Crataegus* increases coronary circulation due to the inhibition of phosphodiesterase action, with a subsequent inhibition of cyclic adenosine monophosphate (cAMP). It also improves myocardial circulation through the enhancement of myocardial energy metabolism [42]. In events of carbondioxide deficiency, *Crataegus* increases myocardial tolerance towards it, thereby increasing cardiac performance [39]. Other activities of *Crataegus* such as antiarrhythmic, hypotensive, hypolipidemic, and antioxidative have also been reported [4, 37, 40]. So many authors have reported the use of different species of *Crataegus* in the management of cardiovascular diseases [5, 21, 22, 28, 29].

With recent scientific breakthroughs, (through in vivo and in vitro studies), which portrayed its antioxidant activities, anti-cardiac remodeling effect, anti-inflammatory effects, decrease of arterial blood pressure effect, endothelial protective effect, lipid-lowering effect, positive inotropic potential, and vasodilating effect among others [22], *Crataegus* might soon be the leading source of treatment for a wide array of diseases. Alternatively, according to Jie Wang *et al*. placebo-controlled trials have reported both objective and subjective amelioration in patients with NYHA classes I-III (mild forms of heart failure), hyperlipidemia, and hypertension [22].

2.2 *Crataegus* berries and congestive heart failure

Reports by Degenring F.H. *et al.* suggested that Crataegisan®, an extract of fresh berries of *C. oxyacantha* L. and *C. monogyna* Jacq. is effective in patients with NYHA cardiac failure class II. With 143 patients as subjects of their study, they discovered a significant improvement of their condition, which they believed to be due to low occurrence of dyspnea and fatigue among the subjects; hence they concluded that under long term therapy with the drug, the patients may experience an improvement in their heart failure condition [9].

2.3 Antimicrobial activity of the fruits

Güven *et al.* reported the antimicrobial activity of the ethyl acetate extracts of the fruits of *Crataegus tanacetifolia* (Lams.) Pres. and *C. bornmülleri* Zabel. were found to possessed varied, broad ranged antimicrobial activity against some human and plant pathogenic microbes, and food toxicants [17].

2.4 Antilipidemic activity

The dried fruits of *Crataegus pinnatifida* Bunge. were found to suppress diet-induced high cholesterol in rats. Kwok Ching-Yee *et al*. investigated the effect of Hawthorn powder by monitoring the plasma lipid profiles and aortic relaxation in Sprague-Dawley rats fed with high-cholesterol diet. In the study, they observed that the consumption of the drug resulted in a significant improvement towards reversing the detrimental changes caused by the diet [6].

2.5 Antioxidant activity

Antioxidant activity of *C. pinnatifida* Bunge. var*. major* fruits was investigated by Tongxun Liu *et al*., and they discovered that the crude drug extract of the Chinese hawthorn had stronger antioxidant activity than the purified one [41]. Earlier, in a pioneer work on the antioxidant activity of the Isreali hawthorn, *Crataegus aronia* (L.) DC. (Syn. *C. azarolus* L., Ljubuncic P. *et al.* reported that a water-soluble decoction made from the leaves and unripe fruits of the plant possessed substantial antioxidant activity as a result of its ability to inhibit:

- Oxidation of β-carotene;
- Lipid peroxidation in rat liver, which was induced by Fe2+;
- Due to its efficient free radical scavenging activity [26].

2.6 Lipid regulating and anti-atherosclerosis effects

Antihyperlipidemic activity of *C. pinnatifida* was reported to be due to hyperin and ursolic acid. Two animal models were administered with the bioactive compounds, and a significant decrease was observed in total cholesterol (TCH); and it was also noticed that the ratio of total cholesterol/high density lipoprotein dropped, thereby reducing the damage caused by oxygen free radical to the vascular endothelium, thus preventing the onset of atherosclerosis [25, 45].

2.7 Antihypertensive effect

In cats, mice, and rabbits, blood pressure could slowly be reduced by *C. pinnatifida* extracts due to the expansion effect of the extracts on the peripheral vessels [10, 44]. Yuan Y *et al*. further corroborated and reported that the extracts could maintain the rat's blood pressure at doses of 1.5 and 2.25 g/kg/day [46].

2.8 Improvement of hepatoactivity

According to M. Veveris *et al*., oral administration of the *Crataegus* special extract (WSR 1442, for 7 consecutive days) exerted cardioprotective effects following transient ischemia and reperfusion, and also prevented myocardial dysfunction and infarction in the test animals [27]. To further elaborate on the cardioprotective effect of hawthorn, Furey A. and Mary C Tassell reported that the effectiveness of the *Crataegus* species against heart diseases is due to their ability to:

- cause peripheral and coronary vasodilation;
- induce positive inotropy, which is independent of cAMP;
- possess antioxidant potentials;
- provide immunity against ventricular arrhythmias that is induced by ischemia;
- show anti-inflammatory activities [16, 24].

2.9 Hepatoprotective activity

M. Veveris *et al*. also discovered the potential of the drug to alleviate the deterioration of cardiac contractile function, as well as its ability to limit the size of infarction and to prevent mortality in rats subjected to a marked insult of 240 min regional myocardial ischemia, followed by 15 min of reperfusion. In addition, they also observed that in a dose-dependent dosage, the herbal remedy also reduced the occurrence of ventricular tachycardias and fibrillations which

correlates with a diminished mortality rate in treated animals [27]. Furthermore, Jie Wang *et al*. reported that in a 2008 Cochrane review on the health effects of hawthorn extract on humans, the extract produced a significant benefit in symptom control as well as physiologic outcomes when used as an adjunctive treatment for chronic heart failure [22, 34].

3. Any effect (s) when taken with synthetic or conventional drugs?

In a study on the interaction of Digoxin® and a preparation of *Crataegus oxyacantha* L., it was discovered and reported that with concomitant administration of digoxin and the hawthorn, there is no significant alteration or change in the pharmacokinetics of digoxin, hence both could be coadministered in the studied dosage [37].

3.1 Adverse events

In a clinical study on the efficacy of two extracts of crataegus (160-1800mg daily, for 324 weeks) standardized to contain 18.75% oligomeric procyanidins and 2.25% flavonoids which involved 5577 subjects, 166 adverse effects (mostly mild to moderate) were reported in all [3]. Dizziness, nausea, fall, gastrointestinal hemorrhage, and erythematous rash were the most frequent among the adverse effects, though headache, migraine and palpitation were also reported. According to the study, none of the patients reported any form of drug interaction [6].

3.2 Toxicity

Hawthorn has been reported to be toxic in high doses. In animal studies, there is no reported case(s) of increase in the frequency of fetal malformations. Though without any reported adverse effects on embryonic development [17], but due to the unavailability of clear data [6] hawthorn extracts or preparations are not advisable during pregnancy and/or lactation.

4. Conclusion

From the information obtained and presented so far, it is evident that members of the genus *Crataegus* possessed numerous, varied, and important pharmacological activities against dreaded diseases. The long term use and investigation of some members of the genus in specific parts of the world is a pointer to the likely emergence of a new drug (from *Crataegus* species), which might be less toxic and more effective than most of the conventional drugs available in the pharmaceutical industries. With more commitment and collaboration, more plants from this genus need to be investigated, a gesture that would lead to the discovery of more n affordable means of treatment and prevention of diseases.

5. References

1. Andrew MS, Elizabeth JW. Hawthorn. *American Literary Scholarship* 2012; 1:37-51.
2. Blumenthal M. The ABC clinical guide to herbs. Austin (TX): *American Botanical Council*, 2003.
3. Jibrin YB. Pharmacognostical analysis of some Nigerian plants with antidiabetic potentials. Thesis (unpublished), Near East University, Turkish Republic of Northern Cyprus, 2016, 1.
4. Chang Q, Zuo Z, Harrison F. *et al*. Hawthorn. *J Clin Pharmacol*. 2002; 42:605-612.
5. Chang W-T, Dao J, Shao Z-H. Hawthorn: potential roles in cardiovascular disease. *The American Journal of Chinese Medicine.* 2005; 33(1):1-10.
6. Ching-Yee K, Candy N-Y W, Mabel Y-C Y, Peter H-F Y, Alice LS A, Christina C-W P *et al*. Consumption of dried fruit of *Crataegus pinnatifida* (hawthorn) suppresses high-cholesterol diet-induced hypercholesterolemia in rats. *Journal of Functional Foods*. 2010; 2:179-186.
7. Claudia D, Gabriela M, Max HP, Edzard E. Adverse-event profile of *Crataegus* spp.: A systematic review. *Drug Safety* 2006; 29(6):523-535.
8. Dahmer S, Scott E. Health effects of hawthorn. *American Family* Physician 2010; 81(4):465-469.
9. Degenring FH, Suter A, Weber M, Saller R. A randomised double blind placebo controlled clinical trial of a standardised extract of fresh *Crataegus* berries (Crataegisan®) in the treatment of patients with congestive heart failure NYHA II. *Phytomedicine* 2003; 10:363–369.
10. Editorial Committee of Modern Clinical Chinese Materia Medica. Modern Clinical Chinese Materia Medica, ed.; *China Press of Traditional Chinese Medicine*: Beijing, China, 1998, 65.
10. European Pharmacopoeia 7.0, Council of Europe, Strasbourg, France, 7th edition, 2007, 1.
11. European Scientific Cooperative on Phytotherapy, Hawthorn leaf and flower, in ESCOP Monographs on the Medicinal Uses of Plant Drugs Exeter, UK., 1999, 1-11.
12. Farnsworth NR, Beecher CWW, Fong HHS. The NAPPALERT database: linking traditional and modern medicine. *Essential Drugs Monitor* 1995; 20:2-3.
13. Folium cum flore crataegi, in WHO Monographs on Selected Medicinal Plants, World Health Organization, Geneva, Switzerland, 2002, 66-82.
14. Fong HHS, Bauman JL. Hawthorn. *J Cardiovasc Nurs.* 2002; 16:1-8.
15. Furey A, Mary T. Towards a systematic scientific approach in the assessment of efficacy of an herbal preparation: Hawthorn (*Crataegus* spp.) *European Journal of Heart Failure* 2008; 10:1153-1157.
16. Güven K, Ersin Y, Ferda C. Antimicrobial Activities of Fruits of *Crataegus* and *Pyrus* Species. *Pharmaceutical Biology* 2006; 44(2):79-83.
17. Hawthorn. In: WHO Monographs on Selected Medicinal Plants. Geneva, Switzerland: World Health Organization, 1999, 1.
18. Horoz M, Gok E, Genctoy G *et al*. *Crataegus orientalis* associated multiorgan hypersensitivity reaction and acute renal failure. *Internal Medicine* 2008; 47(1):2039-2042.
19. Jennifer EE, Paula NB. A review of the chemistry of the genus *Crataegus*. *Phytochemistry* 2012; 79(1):5-26.
20. Jiaqi W, Wei P, Rongxin Q, Hong Z. *Crataegus pinnatifida*: Chemical constituents, pharmacology, and potential applications. *Molecules* 2014; 19:1685-1712.
21. Jie W, Xingjiang X, Bo F. Effect of *Crataegus* usage in cardiovascular disease prevention: An evidence-based approach. *Evidence-Based Complementary and Alternative Medicine*, 2013, Article ID 149363, http://dx.doi.org/10.1155/2013/149363.
22. Koch E, Busse WR, Juretzek W *et al.* "Hawthorn," in Encyclopedia of Dietary Supplements, 2nd edition. *Informa Healthcare*, New York, NY, USA, 2010, 411-422.

23. Krzeminshi T, Chatterjee SS. Ischemia and early reperfusion induced arrhythmias: beneficial effects of an extract of *Crataegus oxyacantha* L. *Pharm Pharmacol Lett* 1993; 3:45-48.
24. Li, GH, Sun, JY, Zhang, XL. Experimental studies on antihyperlipidemia effects of two compositions from hawthorn in mice. *Chin. Tradit. Herbal Drugs*, 2002; 33:50-52.
25. Ljubuncic P, Irina P, Uri C, Hassan A, Arieh B. Antioxidant activity of *Crataegus aronia* aqueous extract used in traditional Arab medicine in Israel. *Journal of Ethnopharmacology*, 2005; 101:153-161.
26. Maris V, Egon K, Chatterjee SS. *Crataegus* special extract WSR 1442 improves cardiac function and reduces infarct size in a rat model of prolonged coronary ischemia and reperfusion. *Life Sciences*, 2004; 74:1945-1955.
27. Mary CT, Rosari K, Deidre G, Mary L, Ambrose F. Hawthorn (*Crataegus* spp.) in the treatment of cardiovascular disease. *Pharmacogn Rev.* 2010; 4(7):32-41.
28. Miller AL. Botanical influences on cardiovascular disease. *Alternative Medicine Review*, 1998; 3(6):422-431.
29. Min BS, Kim YH, Lee SM *et al*. Cytotoxic triterpenes from *Crataegus pinnatifida. Archives of Pharmacol Research* 2000; 23(2):155-158.
30. Newall A, Anderson LA, Philipson JD. Herbal medicines: a guide for healthcare professionals. London: The Pharmaceutical Press, 1996.
31. Palnoki O, Jacomet S. Some aspects of Late Iron Age agriculture based on the first results of anarchaeobotanical investigation at Cprvin ter, Budapest, Hungary. *Veg Hist Archaeobot* 2002; 11:9-15.
32. Pardo-De-Santayana M, Tard´ıo J, Blanco E *et al.* Traditional knowledge of wild edible plants used in the northwest of the Iberian Peninsula (Spain and Portugal): a comparative study. *Journal of Ethnobiology and Ethnomedicine* 2007; 41(5):1-11.
33. Pittler MH, Schmidt K, Ernst E. Hawthorn extract for treating chronic heart failure: meta-analysis of randomized trials. *The American Journal of Medicine*, 2003; 114(8):665-674.
34. Prinz S, Ring A, Huefner A, Pemp E, Kopp B. 4"'-Acetylvitexin-2"-O-rhamnoside, isoorientin, orientin, and 8- methoxykaempferol-3-O-glucoside as markers for the differentiation of *Crataegus monogyna* and *Crataegus pentagyna* from *Crataegus laevigata* (Rosaceae). *Chemistry and Biodiversity*, 2007; 4(12):2920-2931.
35. Rayyan S, Fossen T, Solheim HN, Andersen ØM. Isolation and identification of flavonoids, including flavone rotamers, from the herbal drug (hawthorn). *Phytochemical Analysis* 2005; 16(5):334-341.
36. Rigelsky JM, Sweet BV. Hawthorn: pharmacology and therapeutic uses. *American Journal of Health-System Pharmacy*. 2002; 59(5):417-422.
37. Robert TMS, Helen RT, Daniel SS, Scott GS, Janice LW, Thomas A *et al*. Interaction study between Digoxin and a preparation of Hawthorn (*C. oxyacantha*). *Journal of Clinical Pharmacology,* 2003; 43:637-642.
38. Schussler M, Holz J, Fricke U. Myocardial effects of flavonoids from *Crataegus* species. *Arzneimttel Forschung,* 1995; 45:842-845.
39. Società Italiana di Fitoterapia, Organizzazione Mondiale della Sanità (OMS). Monografie di piante medicinali. Abbiategrasso (Milan), Italy: Le Nuove Scritture, 2004, 2.
40. Tongxun L, Yanni C, Mouming Z. Extraction optimization, purification and antioxidant activity of procyanidins from hawthorn (*C. pinnatifida* Bge. var. major) fruits. *Food Chemistry* 2010; 119:1656-1662.
41. Weiss RF, Fintelmann V. Herbal medicine. New York: Thieme stutgart, 2000.
42. Wittig J, Leipolz I, Graefe EU, Jaki B, Treutter D, Veit M. Quantification of procyanidins in oral herbal medicinal products containing extracts of *Crataegus* species. *Arzneimittel Forschung* 2002; 52(2):89-96.
43. Yang XP. Medicinal value of *Crataegus pinnatifida*. *Jilin Med. J*. 1998; 19:41.
44. Yang YJ, Lin J, Wang CM. Effect of FHL on intervening early hyperlipoidemia model rat. *Chin. Tradit. Herbal Drugs* 2008; 39:1848-1850.
45. Yuan Y, Zhao J, Gao, HJ, Wang JH. Experimental study on effect of hawthorn on compounding hypertension and hyperlipoidemia rats. *J Xinjiang Med. Univ.* 2013; 35:52-27.
46. Zhao HC, Tian BF. China Fruit-Plant Monograph, Hawthorn Flora, Zhongguo Linye Press, Beijing, China, 1996.
47. Geoffrey CK. Medicinal plants and control of parasites. *Trans R Soc Trop Med Hyg.* 1996; 90:605-609.