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Pharmacological and Biological Activities of *Crataegus pentagyna*

Melika Ebrahimzadeh
Amir Mohammad ShahHosseini
Fatemeh Zahra Seyfi

Student Research Committee, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran

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Correspondence:
Fatemeh Zahra Seyfi, Student Research Committee, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran.
Email: fatiima.seify@gmail.com
ORCID: 0009-0003-5055-9259

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ABSTRACT

Due to the numerous side effects of synthetic drugs, people's inclination towards herbal remedies has increased. The hawthorn has been used as food and medicine for centuries. The genus *Crataegus* belongs to the *Rosaceae* family and *Maloideae* sub-family. It is reported this plant has high flavonoid, vitamin C, glycoside, anthocyanin, saponin, tannin, and antioxidant levels. It employed as an anti-inflammatory, gastroprotective, antimicrobial, hepatoprotective agent, hypotensive and diuretic. it is widely used to treat cardiovascular disorders such as arrhythmia, myocardial infarction, and congestive heart failure. This plant is also known to treat diseases such as anti-aging, Alzheimer's, diabetes, cancer, hyperglycemia, hypertension, and anxiety. Iran's flora, *C. pentagyna* subsp. *elburensis* is the most common cultivar of hawthorn. The aim of this review article was to investigate *C. pentagyna* as an important source for treating various diseases. This study focuses on the antioxidant, antimicrobial, vasorelaxant, anti-arrhythmic, anti-hypoxic, photocatalytic effects, and its impact on atherosclerotic Cardiovascular disease and anti-cancer properties of *C. pentagyna*.

Introduction

The genus *Crataegus* is a complex group of trees and shrubs native to northern temperate zones (1), mostly between latitudes 30E and 50E N (2). This plant belongs to the *Rosaceae* family and *Maloideae* sub-family. The genus name *Crataegus*, Rosaceae, is derived from a Greek word *kratos* meaning hardness of wood (3). Hawthorns are native to the Mediterranean region, including north Africa, Europe, and central Asia, but also to many areas of North America (4). It is reported this plant has high flavonoid, vitamin C, glycoside, anthocyanin, saponin, tannin, and antioxidant levels (5,6). 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 (7). This plant employed as an anti-inflammatory, gastroprotective, antimicrobial, hepato-protective agent, hypotensive and diuretic. it is widely used to treat cardiovascular disorders such as arrhythmia, myocardial infarction, and congestive heart failure (4). It is also known to treat diseases such as anti-aging, Alzheimer's, diabetes, cancer, hyperglycemia, hypertension, and anxiety (8,9). *Crataegus* alone consisting of approximately 300 species like *C. monogyna*, *C. orientalis*, *C. curvisephala*, *C. pentagyna*, *C. oxycantha*, *C. azaralus*, *C. prunitifolia*. Iran's flora, *Cr. pentagyna* subsp. *elburensis* is the most common cultivar of hawthorn (10). *C. pentagyna* has few short spines, Leaves ovate, broadly ovate or ovate-rhombic, deeply lobed or separate, erect or raised-bent sepals and black fruits (11). Phytochemical investigations of *C. pentagyna* from different origins have revealed the identification of different compounds such as gallic acid, caffeic acid, and chlorogenic acid in fruit, pulp and seed of Iranian species (12,13). This plant has important properties such as antioxidant, antiradical, antimicrobial and is effective on cardiovascular function, blood pressure, and lipid metabolism. Due to benefits of this plant, we will discuss about its effects.

Antioxidant

Oxidative stress caused by overproduction of free radicals and reactive oxygen species that results in the development of several diseases (10). Antioxidant defenses in organisms against reactive oxygen species produced during normal cell aerobic respiration may be of endogenous or dietary origin (14). Natural antioxidants derived from plants, especially phenolics, are of considerable interest as dietary supplements or food preservatives (15). Plant phenolics are multifunctional and can act as reducing agents, metal chelators and singlet oxygen quenchers (16, 17). Phenolic compounds specially flavonoids have ability to inhibit oxidases, increase the availability of endogenous antioxidants and the activity of antioxidant enzymes (16). Due to the hydroxyl (-OH) and methoxy (-OCH3) groups in their molecular structures, phenolic compounds possess the ability to scavenge free radicals (10). It has been proven in various studies that *C. pentagyna* has significant antioxidant effects. Antioxidant activities of *C.pentagyna* extracts were attributed to the major phenolics and terpenes detected by HPLC-MS/MS and GC-MS. It was characterized 62 compounds including mainly flavone apigenin, phenolic acid salicylic acid and flavanone naringin in fruit, leaf and root, respectively.

Also, bioactive compounds such as alkane nonacosane in fruit and leaf extracts and trit-erpene squalene in root extract were identified using GC-MS as major components (10). The fruit extract with the highest phenolic and flavonoid content exhibited the highest DPPH radical scavenging capacity (IC50 = 15.43 ± 0.65 g/mL), followed by leaf and root extracts (IC50 = 34.67 ± 0.14 g/mL and 60.72 ± 0.32 g/mL, respectively) (10). Iron is capable of generating free radicals from peroxides by Fenton reactions. Ferrozine can form complex with Fe^{2+}. In the presence of other chelating agents, the complex formation is disrupted with the result that the red color of the complex decreases. Extract interfered with the formation of complex, suggesting that it has chelating activity and captures Fe^{2+} before ferrozine(17).

In *Rabiei et al.* study fruit extracts of this plant exhibited good H_2O_2 radical scavenging and Fe^{2+} chelating ability (17). Free radical scavenging activity, Ferrous ion chelating activity and 15-Lipoxygenase inhibition of *C. pentagyna* extracts were investigated and It was proven that extracts scavenged hydroxyl radical with comparable EC50 values (0.86±0.05 mg/mL for flower extract; 0.9±0.0 mg/mL for leaf extract), Flower and leaf extracts chelated ferrous ions with EC 50 values of 1.9±0.0 and 1.3±0.0 mg/mL, respectively and leaf extract showed a higher inhibitory activity towards 15-lipoxygenase than flower extract (129.63±0.75 and 151.76±1.65 µg/mL, respectively (18). Also, the antioxidant properties of extracts from *C. pentagyna*, from fruits and sprig (branchlets) were assessed by flow cytometry for potential applications in blood storage (19). In *Ebrahimzadeh et al* study, the antioxidant activity of CP fruits methanol and aqueous extracts was examined, employing various in

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vitro assay systems, such as DPPH and nitric oxide radical scavenging, reducing power, linoleic acid and iron ion chelating power. Based on total phenol contents, it was shown that aqueous extract had higher DPPH-scavenging activity than methanol one. In the reducing power assay, the presence of reductants (antioxidants) in the samples would result in the reducing of Fe^{3+} to Fe^{2+} by donating an electron. The extracts showed weak nitric oxide-scavenging activity between 50 and 800 ug mL^{-1}. It was found that the reducing powers of extracts and the % inhibition increased with the increase of their concentrations. Neither extracts showed good Fe^{2+} chelating ability. Results suggesting that their actions as an antioxidant may not be related to their iron binding capacity (20) *ŻUREK at el* study aimed to characterize the biological activity of individual morphological parts collected from different species of this plant. The results showed that the strongest antioxidant properties through various reaction mechanisms were assessed for berries, mainly of the species C. laevigata x rhipidophylla x monogyna. In turn, flowers were statistically the weakest in terms of antioxidant potential (21).

Antimicrobial

According to research, flavonoids affect microbial gene expression, inhibit microbial enzymes, and disrupt the integrity of microbial cell membranes (22). Membrane disruption by terpenoids and phenolics and metal chelation by phenols and flavonoids are thought to inhibit growth of microorganisms (23). Study the antibacterial activities of petroleum ether and hydro-methanolic extracts of *C. pentagyna* fruit, leaf, and root against two pathogenic bacteria (Staphylococcus aureus and Escherichia coli) shows that extracts inhibited bacterial growth with MIC and MBC values ranging from 0.15 to 5.12 mg/mL and 0.15 to 10.12 mg/mL, respectively (10). The fruit hydro-methanolic extract exhibited the highest levels of antibacterial activity, followed by the leaf and root extracts (10). The presence of terpenes and flavonoids explains the high antibacterial activity in petroleum ether and hydro-methanol extracts of extracts, respectively (10). Study shows that both pulp and seed extracts displayed relatively high antibacterial activity against Escherichia coli (ATCC8739) and Salmonella enterica (ATCC 19430), which belong to Gram-negative strains, and Bacillus cereus (ATCC 11778) and Staphylococcus aureus (ATCC 6538), which are Gram-positive strains. MIC and MBC values in this study revealed that pulp and seed extract of *C. pentagyna* have significant antibacterial activity (13). Antibacterial activity wool yarn (1g) dyed with *C. pentagyna* in optimal dyeing condition was evaluated against both S. aureus and E. coli bacteria, and the results show antibacterial properties against both types of bacteria. It is also evident that the antibacterial activity against E. coli was greater than that of S. aureus due to the differences in the structure of bacteri (24). In another study, acetonic extract of fruits were examined and has most efficient bactericidal activity against *Bacillus subtilis* (MBC= 2.5 mg/ml) while *Salmonella enteric* was the most resistant bacterium (MBC= 20 mg/ml) (25). Gram-positive bacteria are more sensitive than Gram-negative bacteria. In addition to the peptidoglycan layer, Gram-negative bacteria have an outer membrane in their cell walls. This hydrophilic outer membrane, rich in lipopolysaccharide molecules, acts as a barrier against antibiotics. However, in the case of Gram-positive bacteria, antimicrobial agents easily penetrate the cell wall and membrane, leading to the destruction of the cytoplasm and its coagulation (26). This explains the higher MBC of the willow extract against Gram-negative bacteria compared to Gram-positive types. Studies on the antimicrobial activity of various pomegranate peel extracts have reported that the acetone extract has the highest antimicrobial properties, attributed to the presence of active phenolic and flavonoid compounds in the extract of this plant (27). The antibacterial potential of the synthesized silver nanoparticles using fruit extract of C.

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pentagyna (CP-AgNPs) as reducing agent and capping agent were investigated using micro broth dilution method which showed well inhibitory effect against seven ATCC strains of bacteria and eight strains of drug-resistant bacteria. Due to the results, CP-AgNPs enhanced antimicrobial potential against S. aureus (0.11, 7.1 µg/ml), E. faecalis (0.11, 1.7 µg/ml), P. aeruginosa (0.11, 0.22 µg/ml), A. baumannii (0.11, 0.22 µg/ml) and E. coli (0.11, 0.44 µg/ml) for MIC and MBC, respectively. The highest MIC were observed for P. mirabilis bacteria with 0.89 µg/ml and 14 µg/ml for MBC and after that K. pneumonia with MIC 7.1 µg/ml and MBC 57 µg/ml (28).

Vasorelaxant effects

Extract of *Crataegus* leaves with flowers induces an endothelium-dependent, NO-mediated vasorelaxation via eNOS phosphorylation (29). NO, a strong vasodilator, is generated from L-arginine substrate by endothelial NO synthase (eNOS). Arginase is an enzyme expressed in both endothelial and vascular smooth muscle cells (30), which converts L-arginine into urea and polyamines. More than half of NO available in the human body derives from L-arginine. At endothelial level, arginase and eNOS compete for the same substrate, L-arginine. Thus, arginase is indirectly responsible for the decrease in NO bioavailability (31). Substances from plants have great potential to be applied as arginase inhibitors, most of which are polyphenols. Of the relevant mechanisms in this process, the inhibition of arginase by natural products seems to act against endothelial dysfunction by reestablishing the vascular function and elevating nitric oxide levels (by increasing the amounts of substrate (L-arginine, and endothelial nitric oxide synthase activation and stabilisation) as well as decreasing the generation of reactive species (formed by uncoupledendothelial nitric oxide synthase (32).In the study of *Bujor et al*, it was proved that all *C. pentagyna* extracts showed significant inhibitory effects towards arginase, all *C.pentagyna* extracts exhibited vasorelaxant effects mediated mainly by NO and additionally by inhibition of Ca2+ channels in case of CPFlextract, and chlorogenic and neochlorogenic acids and epicatechin predominated among the quantified polyphenols (33).

Antiarrhythmic

It has been shown that different flavonoid constituents of the *Crataegus* extract might affect the cardiovascular system dissimilarly. Some flavonoids increased heart rate, coronary flow, and left ventricular pressure, while others had negative chronotropic effects or exerted no function. An increase of coronary flow caused by the O-glycosides luteolin-7-glucoside (186%), hyperoside (66%) and rutin (66%) as well as an increase of the relaxation velocity (positive lusitropism) by luteolin-7-glucoside (104%), hyperoside (62%) and rutin (73%) were the major effects observed at a maximum concentration of 0.5 mmol/l. Furthermore, slight positive inotropic effects and a rise in heart rate were seen. Similar but less intensive actions were found with the C-glycosides vitexin, vitexin-rhamnoside and monoacetyl-vitexin-rhamnoside (34). The cardiac effects of *C. pentagyna* leaf extract using cardiomyocytes (CMs) differentiated from healthy human embryonic stem cells, long QT syndrome type 2 (LQTS2), and catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1) patient-specific induced pluripotent stem cells was studied. Results show *C. pentagyna* leaf extract and its isoquercetin and vitexin flavonoids may be introduced as a novel nutraceutical with antiarrhythmic potential for CPVT1 patients (35). The results suggest an inhibition of 3',5'-cyclic adenosine monophosphate phosphor-diesterase as the possible underlying mechanism of cardiac action of flavonoids from Crataegus species (34).

Antihypoxic

Hypoxia, a state of oxygen deficiency, mediates the production of nitric oxide, which in turn provokes lipid peroxidation and cell membrane injury (36). Effect of HLF

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(Hawthorn leave flavonoids, w/w, 80% flavonoids) on hypoxia-treated human umbilical vein endothelial cell (HUVECs) was studied to evaluate the potential effect of HLF against thrombus formation. Data from this study showed that HLF decreased the cytotoxicity of hypoxia to HUVECs through its regulative effect on decreasing the intracellular levels of NO and calcium ion (37). Also studies show that polyphenolic compounds that are found in this plant cause anti-hypoxic activity. Actually the extracts postponed hypoxia in a dose-dependent manner. *C. pentagyna* (at 100 mg/kg) was found to be the most effective extract against circulatory hypoxia (38).

Photocatalytic activity:

Water contamination caused by recalcitrant organic pollutants, such as organic dyes, pesticides and antibiotics, affects seriously the quality of water resource and human health. Thus, decomposition of these organic dyes is of great significance to water purification and conservation (39). Heterogeneous photocatalysis decomposes recalcitrant organic pollutants including organic dyes in water (39) through breaking down the organic compounds into simple molecules such as carbon dioxide and water (40). The main advantage of photocatalysis is that there is no further requirement for secondary disposal methods. Other treatment methods such as adsorption by activated carbon and air stripping merely concentrate the chemicals present by transferring them to the adsorbent or air and they do not convert them to non-toxic wastes (40). Study shows Ag particles that have been obtained through facile and rapid sonochemical method in presence of *C. pentagyna* extract as a green capping agent and reducing agent have remarkable effect on catalytic activity of Fe/Si/Cu_2O–Ag photocatalyst for degradation. It is observed that influence of the ratio of Ag:Fe/Si–Cu (0.9:1) and C. pentagyna as a reducing agent and capping agent are very effective to synthesis fine and homogenous spherical Fe/Si/Cu–Ag nanocomposites. The photocatalytic activities of as-prepared Fe/Si/Cu–Ag nanocomposites have been calculated with employing the methylene blue (MB) and rhodamine b (RhB) contaminants solution and the percentage degradation of methylene blue and rhodamine b pollutants percentage was measured by the amount of contaminants adsorbed of catalyst (40). Due to the catalytic results can be demonstrated that C.pentagyna mediated AgNPs have well photocatalytic activity and could be efficiency for degradation of organic contaminants such as rhodamine b, eosin and methylene blue (28). It can be concluded that these nanocatalyst can be used as an efficient magnetic base photocatalyst in the water treatment field (41).

Atherosclerotic Cardiovascular disease

The main and effective factor in atherosclerotic cardiovascular disease (CVD) is the accumulation of cholesterol in arterial macrophage (42). Nowadays, due to the many side effects of chemical drugs, the tendency to use herbal sources has increased. Some suitable medicinal herbs such as Crataegus species (Hawthorn) are introduced as promoter of cardiovascular function and health and are suitable for cardiovascular disease (43). Hawthorn has been found to decrease the serum levels of cholesterol, LDL-cholesterol, and triglyceride in hypercholesterolemic and atherosclerotic animals (44). One possibility mechanism is the up-regulation of the hepatic LDL receptors (43). Another one is inhibiting the oxidative modification of LDL cholesterol and thus prevent the associated cytotoxicity due to being rich in flavonoids (44). Previous researches show that main compositions of the C. pentaegyna sample were oleic acid (13.44%), palmitic acid (7.72%), linoleic acid (22.43%) and arashidic acid (0.47%) which are known as natural ligands for PPAR-α (43). PAR- α is highly expressed in tissues (liver, kidney, heart, muscle, adipose tissue) with high rates of fatty acid catabolism, and PPAR- α activators increase 'reverse cholesterol transport' by accelerating the efflux of cholesterol from peripheral cells and increasing its uptake into liver through a

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pathway involving increased vascular expression of the HDL-c receptors, ATP-binding cassette transporter-I (ABC-I) and scavenger receptor class-B type-I (SR-BI) (45). The uptake of additional cholesterol from macrophage foam cells by HDL and ApoAI is considered one of the most important protective mechanisms of HDL against atherosclerosis and the membrane lipid translocases ABCA1 and ABCG1, are the main markers of plasma HDL levels and they represent important protective factors against atherosclerosis (46). It is well known that ABCA1 is the initiator element of reverse cholesterol transport (RCT) process which plays a crucial role in HDL biogenesis, maturation, and its plasmatic formation (47). In conclusion C. pentaegyna can inhibit the progression of premature atherosclerosis by increase gene ABCA1 expression (42). Data indicate that C. pentaegyna extraction induced an exercise-like effect on ABCA1 mRNA expression at rest, while it showed opposite response to high intensity treadmill running program (47).

Anticancer

Angiogenesis is a process that can be classified into physiological and pathophysiological forms. Physiological angiogenesis, which is a strongly regulated process, occurs in such cases as wound healing, placental growth, and ovulation. However, pathophysiological angiogenesis, which refers to the uncontrollable proliferation of capillary endothelium, is seen in such diseases as diabetic retinopathy, atherosclerosis, growth, and metastases of tumors (48). other. Collagen XVIII is the molecule of such fragments as TSP-1 and endostatin that can control the anti-angiogenesis activity, proliferation of cells, and apoptosis, and it can be assumed to regulate the development of vascular system (49). The increase in the amount of collagen XVIII can possibly lead to an increase in the performance of collagen XVIII /endostatin mechanisms, and inhibit the growth of endothelial cells, inhibit angiogenesis, weaken different cancers and the growth of tumors (50). In *Abdi et al.* study, the black crataegus extract led to an insignificant increase of plasma collagen XVIII. This effect is due to the quercetin that is one of the flavonoids found in plants, which has various effects including anti-tumor properties. The anti-tumor effects of quercetin are related to its ability to inhibit the angiogenesis of tumor through the inhibition of migration and growth of endothelial cells (49). Quercetin decreases the expression of MMP-2 and inhibits the formation of endothelial enzyme of nitric oxide synthase, through the kinase protein activated by mitogen, c-Jun NH2 kinase, and focal adhesion kinase, and the expression and activation of MMP-2 (51). In general, researchers concluded that the increase of collagen XVIII (albeit insignificant) as a result of physical activity and consumption of black crataegus extract could possibly serve as a regional inhibitor of angiogenesis and another evidence for the anti-cancer effects of physical activities (49).

Conclusion

In general, *C. pentagyna* is considered as a valuable natural resource due to its beneficial effects, which can be used in diseases such as cardiovascular disorders and could be useful for the drug industry. It is suggested that further research should be conducted.

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Conflicts of interest

The authors declare no conflict of interest.

Authors' contributions

All authors were involved in the conception and design, analysis and interpretation of the data, drafting of the manuscript and revising it critically for intellectual content, approved the final version for submission, and agreed to be accountable for all aspects of the work.

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