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HAWTHORN, A PROMISING PLANT WITH DIVERSE BIOMEDICAL APPLICATIONS

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ABSTRACT

Hawthorn (*Crataegus* species) is distributed widely in Asia, North America and Europe. The fruits and leaves of hawthorn have been used to treat many health conditions. Many *in vivo* and *in vitro* studies have been carried out for its biomedical applications. Hawthorn extract possesses a range of different activities including, antioxidant, antibacterial, anti-inflammatory, anticataract, hypolipidemic, hypotensive, and anticancer activities. The present review aims to give a detailed understanding of the morphology, chemical composition, pharmacological and biomedical activities of Hawthorn. Phytochemicals like flavonoids, procyanidins, catecholamines, polysaccharides, triterpenes, have been identified evaluated for biological activities. In addition, this review discusses the clinical trials of various Crataegus plants along with the scope for future research in this aspect.

Keywords: Hawthorn, *Crataegus*, antioxidant, anti-inflammatory, antibacterial, anticancer

INTRODUCTION

For many centuries, the medicinal properties of hawthorn have been used to cure many diseases in different systems of medicine. Hawthorn is a thorny tree, which belongs to the *Rosacea* family and over than 1000 species are expanded in mild regions including, North America, East Asia, and Europe **(Hatipoğlu *et al.*, 2015)**. The major species of Hawthorn are *Crataegus oxyacantha*, *Crataegus monogyna*, *Crataegus pentagyna* which are found in Europe, *Crataegus azarolus* is found in the Mediterranean region, *Crataegus mexicana* is known in Mexico, and *Crataegus greggiana* is found in North America. Hawthorn fruits are processed into candies, canned fruits, jellies, jams and soft drinks **(Hatipoğlu *et al.*, 2015)**. Hawthorn plays important roles in regulating blood sugar level, improving immune system, and reducing inflammation (Y. Niu et al., 2013)**.** In addition, it is highly effective in treating cardiovascular disease, hypertension, hyperlipidemia, reducing anxiety, stress, insomnia, and improving digestive problems **(Hatipoğlu *et al.*, 2015)**. Also, it acts as diuretic, hypotensive, cardiotonic, antispasmodic, and anti-atherosclerotic agent **(Chang *et al*., 2002).**

MORPHOLOGY OF HAWTHORN

The hawthorn (*Crataegus* spp.) belongs to *Rosaceae* family. It is multi-branched with height that can reach up to 10 m. Hawthorn fruits mature in late summer as bright-colour berries, blackish-purple, yellow, or deep red colour fruits **(Huang *et al.*, 2013).**

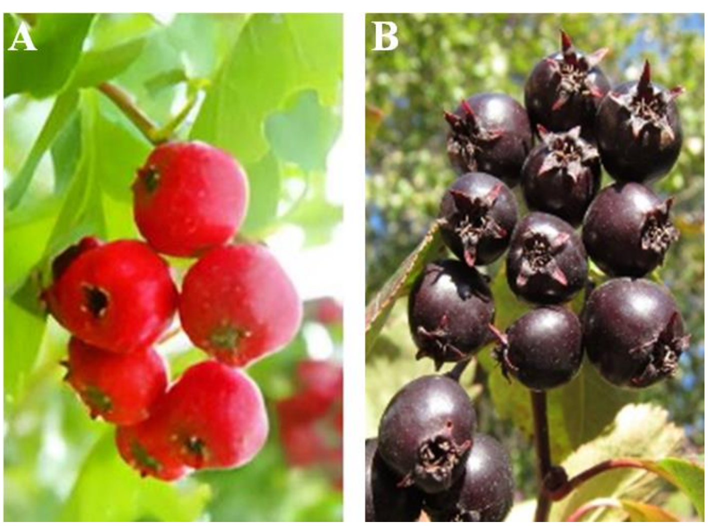

Figure 1 Hawthorn Fruits. **A)** *Crataegus pinnatifida*, **B)** *Crataegus douglasii*: *Rhaphiolepis* Hawthorn **(Huang *et al*., 2013)**

CHEMICAL COMPOSITION OF HAWTHORN

Phenolic compounds have been identified and reported in different species of hawthorn. The reported phenolic compounds include procyanidins, flavanals, flavonols, phenolic acids, anthocyanin, C-glycosyl flavones, vitamin C, saponin, and tannin **(Ljubuncic *et al., 2005; Liu et al., 2011a).*** Procyanidin consists of epicatechin, procyanidin B2, procyanidin B5 and procyanidin C1. These procyanidins are found in *C. pinnatifida*, *C. Scabrifolia*, and *C. brettschneideri* fruits **(Liu, 2012)**. Quercetin, sexangularetin, and kaempferol are the major flavonol aglycons, while rutin, isoquercitrin, hyperoside, kaempferol-3-O-neohesperidoside, spiraeoside, and crataegide are the major flavonol glycosides **(Liu, 2012).** Luteolin and apigenin are the derivatives of C-glycosyl flavones. The most common C-glycosyl flavones are vitexin and its derivatives. Vitexin and isovitexin are in flowers of *C. monogyna, C. laevigata*, and *C. pentagyna* **(Liu, 2012)**. Leaves and fruits of all species of hawthorn contain chlorogenic acid. Caffeic acid is found in the leaves of *C. laevigata*, while the gallic acid and hydroxybenzoic acid are found in the leaves of *C. cuneate*. Protocatechuic acid found in the fruits of *C. pinnatifida* **(Liu *et al.*, 2011a; Svedström *et al*., 2006; Ma and Gu, 2003; Ma *et al*., 2007).**
High performance liquid chromatography (HPLC) combined with mass spectrometry revealed the phenolic compounds in hawthorn. In the flowering tops of the European Hawthorn, the flavonoids content was in the range of 3-19 g/kg dry mass **(Peschel *et al*., 2008).** The content of total procyanidin was 23 g/kg dry mass (92% of total phenolic compounds), while the epicatechin content was 8 g/kg dry mass. The content of procyanidins varied between different species of *Crataegus*; in the fruits of *C. pinnatifida*, *C. cuneata*, *C. kansuensis*, and *C. hupehensis* were 18, 27, 40, and 52 g/kg dry mass, respectively. The major flavonol glycosides in *C. pinnatifida* were hyperoside (1g/kg dry mass) and isoquercitrin (less than 1 g/kg dry mass), while the major phenolic acid was the chlorogenic acid (up to 2 g/kg dry mass) **(Cui *et al*., 2006a).** In hawthorn fruits, the major triterpene acids are oleanolic acid and ursolic acid **(Zou and Chen, 2006).** The contents of ursolic acid and oleanolic acid in the *C. cuneata* fruits were 2.2 g/kg and 24g/kg dry mass, respectively **(Zou and Chen, 2006).**

HEALTH BENEFITS OF HAWTHORN

The physiological effects and biological activities of hawthorn have been investigated in the past few decades.

Antibacterial activity

The antibacterial activity of hawthorn was studied by using the agar well diffusion method. A clear inhibition of the growth of *S. aureus*, *B. subtilis*, and *L. monocytogenes* was observed by extract concentrations of 1.25, 10, and 5 µg/ml, respectively. The methanolic extract of *Crataegus pinnatifida* exhibited a clear inhibition towards Gram negative bacteria (*E. coli*, *S. castellani*, *S. typhimurium*, and *P. aeruginosa*) with concentrations of 10, 10, 1.25, and 20 µg/ml, respectively **(Zhang *et a*l., 2020)**. *C. pinnatifida* showed an antibacterial activity against *E. coli*

(0.98 mg/ml), *G. vaginalis* (1.95 mg/ml), *S. aureus* (0.98 mg/ ml), and *P. aeruginosa* (0.49 mg/ ml). 4-ethyl-2-methoxyphenol of hawthorn inhibits bacterial growth by preventing biofilm formation, moreover, the aldehydes of the plant has a broad spectrum of activity against bacteria via the formation of reactive oxygen species that led to the disruption of the nucleic acids, proteins, and cell organelles of microorganisms **(Rao *et al.*, 2019)**. *C. elbursensis* seed extract showed a bacteriostatic activity against *S. aureus* (10 mg/ml), *B. cereus* (10 mg/ ml), *E. coli* (40 mg/ml), and *S. enterica* (20 mg/ml). Many studies reported that Gram positive bacteria are more susceptible to the hawthorn extract than Gram negative bacteria and this may be due to the difference in the cell wall structure of bacteria ***(*Salmanian *et al., n.d.).***

In addition, the inhibition of the growth of *S. aureus* (Minimum inhibitory concentration (MIC) (5 mg/ml) and Minimum bactericidal concentration (MBC) (100 mg/ml) by the aqueous extract of hawthorn as well as by the ethanolic extract of hawthorn (MIC = 2.5 mg/ml and MBC = 50 mg/ml)) have been reported previously (**Niu *et al*., 2013)**. It was related to the main phenolic compounds found in the plant. The antimicrobial action by the phenolic compounds may occur by different mechanisms, by the disruption of the bacterial membrane via the interactions of the flavonoids in the extract, especially catechins, with the hydrophobic molecules in the interior of the bacterial membrane. This interaction can cause a change in the structure of the membrane and can inhibits/inactivates the synthesis of the intracellular and extracellular enzymes. In addition, flavonoids can reduce fluidity and flexibility in hydrophilic and hydrophobic regions of the both inner and outer cellular membrane. This makes the membrane rigid and difficult to translocate the components across it **(Zhang *et al*., 2020).** Moreover, the flavonoids may inhibit topoisomerase enzymes, this enzyme normally manages DNA supercoils in order to prevent stress, and inhibits the helicase involved in DNA replication, hence the inhibition of bacterial dividing and other biological processes. Another mechanism that could explain the antibacterial activity of hawthorn was related to the dehydrofolate reductase (DHFR) that is important for folic acid synthesis, the epigallocatechin gallate (EGCG), ester of gallic acid and epigallocatechin that belongs to catechin class of phytochemical. EGCG is a potent free radical scavenger and antioxidant, and can inhibit DHFR which had a synergistic effect with sulfamethoxazole (SXT). SXT and trimethoprim combination is used to treat urinary tract infections. EGCG inhibits not only the bacterial growth, but also suppresses the expression of specific genes related to biofilm formation **(Zhang *et al*., 2020).**

Table 1 Antibacterial activity of hawthorn against different microorganisms

Hawthorn (organ)	Concentration	Susceptible Microorganism	Reference
C. pinnatifida (Seeds)	0.98 mg/ml	*E. coli*	**(Rao *et al.*, 2019)**
	1.95 mg/ml	*G. vaginalis*	
	0.98 mg/ml	*S. aureus*	
	0.49 mg/ml	*P. aeruginosa*	
C. elbursensis (Fruits)	10 mg/ml	*S. aureus*	**(Salmanian *et al.*, 2014.)**
	10 mg/ml	*B. cereus*	
	40 mg/ml	*E. coli*	
	20 mg/ml	*S. Enterica*	
C. tanacetifolia (Leaves)	6.16 mg/ml	*B. subtilis*	**(Benli *et al*., 2008)**
	< 394 mg/ml	*Shigella*	
	3.08 mg/ml	*L. monocytogenes*	
	> 3.08 mg/ ml	*S. aureus*	
C. pinnatifida (Fruits)	1.25 µg/ml	*S. aureus*	**(Zhang *et al*., 2020)**
	10 µg/ml	*B. subtilis*	
	5 µg/ml	*L. monocytogenes*	
	10 µg/ml	*E. coli*	
	10 µg/ml	*S. castellani*	

Anticancer activity

Many *in vitro* studies demonstrated the anti-cancer activity of hawthorn extracts. The homogenous polysaccharide (HPS) from hawthorn extracts induced cell apoptosis and arrested cell cycle after administration at a concentration of 125-1000 µg/ml against human colon cancer cell line HCT-116. It exhibited anticancer activity through intrinsic and extrinsic mechanisms PI3K/mTOR signaling pathway **(Ma *et al.*, 2020)**. Moreover, hawthorn fruit extract showed an antioxidant activity and cytotoxic effects against tumour cells, the breast cancer cell line (MCF-7) and the ovarian cancer cell line (SK-ov-3) with IC_{50} 2.76 µg/ml and 11.72 µg/ml, respectively. Selenium nanoparticles from hawthorn extracts induced a mitochondrial dysfunction and oxidative stress that resulted in the apoptosis of liver cancer cells (HepG2) **(Cui *et al*., 2018)**. The cytotoxic activity of triterpenes extracted from *C. pinnatifida* was evident against different cancer cell lines including; Sk-ov-3, lung cancer cell line (A549), Glioblastoma (XF498), colorectal adenocarcinoma **(**HCT-15), and mouse lymphocytic leukemia cells (L1210) **(Zhao *et al.*, 2019).** Quercetin 3-o-galactoside and kaempferol-3-o-glucoside inhibited MCF-7 cell while crataquinone A isolated from *C. pinnatifida* exhibited cytotoxic effects against liver Hep3G2 and Hep3B cell lines **(Zhao *et al.*, 2019).** The treatment with flavonoids (150 mg/kg) isolated from hawthorn extract decreased the weight and volume of induced tumours in mice **(Nazhand *et al.*, 2020)**. 8-*O*-4′ neolignans isolated from hawthorn extract showed a range of anticancer activity against different cell lines. 8-*O*-4′ neolignans was cytotoxic to the histiocytic lymphoma U937 (IC_{50}= 2.71 µM), HepG2 (IC_{50}= 39.97 µM), HCT-116 (IC_{50}= 26.35 µM), human fibrosarcoma cell line HT-1080 (IC50= 31.93 µM), and fetal lung fibroblast-like cells Mrc-5 (IC_{50} > 50 µM) **(Huang *et al*., 2013).**

Table 2 Anti-cancer activity of Hawthorn extract.

Hawthorn (organ)	Extract	Concentration	Cell line	Reference
C. pinnatifida (Fruits)	Selenium	19.22 ± 5.3 µg/mL	HepG2	**(Cui *et al*., 2018)**
***C. pinnatifida* (Fruits)**	Phenylpropanoid	24.90 µM	Hep3B	**(Zhao *et al*., 2019)**
	Dibenzofuran	12.24 µM	HepG2	
***C. pinnatifida* (Seeds)**	8-O-4′ neolignans	2.71 µM	U937	**(Huang *et al*., 2013)**
		39.97 µM	HepG2	
		26.35 µM	HCT116	
		31.93 µM	HT1080	
		> 50 µM	Mrc5	

Antioxidant activity

The main species of *Crataegus* that exhibit an antioxidant activity were *C. folium and C. pentagyna* **(Kumar *et al.*, 2012)**. The antioxidant activity of hawthorn has been demonstrated in many studies. The main compounds with strong radical scavenging activities in *C. azarolus* were hyperoside, chlorogenic acid, isoquercitrin, quercetin, procyanidin B2, and epicatechin **(Liu, 2012)**. Moreover, the ethanolic extract of *C. monogyna* fruits showed greater radical scavenging activities than its aqueous extract. Ethyl acetate exhibited greater inhibitory effects on tyrosinase and greater radical scavenging activity than the ethanolic extract which may be due to its ethyl acetate which is significantly 10 times higher than that of the ethanolic extract. In addition, *C. microphylla* extract exhibited a radioprotective effect against induced-toxicity by irradiation in bone marrow cells **(Liu, 2012).** Moreover, Alirezalu *et al.* reported that the antioxidant capacity of *Crataegus* species varied with different organs of the plant and range from 0.9 to 4.65 mmol Fe^{++}/g DW plant. Also, the leaves of *C. pentagyna* showed the highest antioxidant activity whereas the lowest activity was reported with the use of the extract from the leaves of *C. azarolus.* In addition, some environmental stresses like drought and cold increase the antioxidant activity (Alirezalu *et al*., 2018). Garcia-Mateos *et al*. showed that the antioxidant activity of hawthorn fruits not only associated with the presence of flavonoids and phenolic compounds; however it is also related to other metabolites like vitamin c and carotenoids (García-Mateos *et al*., 2013). Additionally, the hawthorn polyphenol prepared by ethyl acetate treatment of the ethanolic extract of the Chinese hawthorn fruit *C. pinnatifida* revealed strong O_2^- and *OH scavenging capacities, as well as selective prolyl endopeptidase inhibition. The ethyl acetate fraction showed a higher radical scavenging activity than that of the ethanolic extract. Also, the ethyl acetate fraction inhibited the tyrosinase and lipoxygenase activities. (Cui *et al.,* 2006b).

Anti-inflammatory activities

The flavonoid extract from *C. pinnatifida* fruits reduced the production of prostaglandin and nitric oxide (NO). Prostaglandins are the products of Cox2 which is stimulated by lipopolysaccharide, and leads to swelling and pain with inflammation, while the NO which is produced by nitric oxide synthase (NOS) regulates the expression of the proinflammatory cytokines IL-6, IL-1B, TNF-α which correlate with Type 2 *Diabetes Mellitus* (T2DM) and insulin resistance **(Liu, 2012)**. The treatment with 50-200 mg/kg/day of a flavonoid extract for 5 days alleviated the increase of AST and ALT, liver necrosis, and attenuated neutrophil infiltration induced by lipopolysaccharide **(Kumar *et al*., 2012).**

Due to exposure of various endogenous and exogenous stimulants, NOS expression can be produced in macrophages and smooth muscle. The inflammatory process is an outcome of the increased production of NO and expression of NOS. NOS inhibitors may prevent inflammation induced by toxins **(Zhang *et al*., 2020).** The overproduction of NO during the inflammatory response may lead to cytotoxicity and tissue damage. NO have a major role in diabetes, Parkinson’s disease, atherosclerosis, and septic shock. In addition, TNF-α is an important mediator in defense and apoptosis induction. It stimulates the production of IL-6, IL-1β, adhesion molecules and collagenase. IL-1β is a proinflammatory mediator released by macrophage and had an important role in rheumatoid arthritis pathophysiology. IL-6 is a mediator of LPS that induced fever. Hawthorn fruits inhibited the production of NO and expression of TNF-α ,IL-6, IL-1β, and Cox2) in the monocyte/macrophage-like cells, RAW 264.7 **(Li & Wang, 2011**). Moreover, neolignams isolated from the ethanolic extract of hawthorn exhibited antioxidant and anti-inflammatory properties by inhibiting TNF-α and NO **(Liu, 2012).**

Hypolipidaemic activity

The main species of *Crataegus* which play an important role in lowering lipids are *C. laevigata and C. pinnatifida* **(Kuo *et al*., 2009)**. The effective compounds for the hypolipidaemic effects of hawthorn extracts are quercetin, hyperoside, chlorogenic acid, and rutin **(Ye *et al*., 2010**). Rats on high-fat diet when treated with hawthorn extract revealed the hypolipidaemic effects of hawthorn. A decrease in the plasma level of LDL cholesterol and an increase in the plasma level of HDL cholesterol were reported. The hypolipidaemic effects of hawthorn extracts may be via different mechanisms. The extracts enhanced LDL clearance from plasma, reduced cholesterol biosynthesis by inhibiting 3-Hydroxy-3-Methylglutaryl-Coenzym-A (HMG-CoA) reductase activity and by upregulating 7-alpha-hydroxylase enzyme activity **(Rajendran *et al.*, 1996).**

Hypotensive effects

The hypotensive effects of hawthorn have been demonstrated in many clinical studies and in animal models. Hawthorn extract inhibited the NG-Nitro-l-Arginine Methyl Ester (L-NAME), a non-selective NOS inhibitor with hypertensive properties. L-NAME prevents the production of NO by inhibiting NOS-induced hypertension. The major fraction of hawthorn involved in hypotensive effects was the hyperoside, which is a type of flavonoid and provides a protective effect against oxidative stress. The infusion of 6 mg/kg/day of hyperoside and 100 mg/kg/day of aqueous extract of the leaves of *C. tanacetifolia* to L-NAME-treated rats revealed a decrease in blood pressure and alleviated coronary blood vessels thickness caused by L-NAME treatment. Many studies demonstrated that 1200 mg of hawthorn for 16 weeks daily have decreased the systolic and diastolic blood pressure in patients with hypertension **(Asgary *et al*., 2004; Kumar *et al*., 2012).**

Hypoglycemic activity

Diabetes mellitus is a complex metabolic disorder affecting people all over the world. About 415 million adults between the age of 20 and 79 years were affected by diabetes. The researchers expected that by 2040 around 642 million adults will have diabetes. T2DM leads to many complications like neuropathy, nephropathy, retinopathy and atherosclerosis **(Aierken *et al*., 2017)**. *Crataegus* extract is used to treat T2DM, tannins and flavonoids act as anti-diabetic agents **(Aierken *et al*., 2017)**. Hawthorn regulates diabetes and obesity by decreasing blood glucose level and increasing insulin levels. And it plays an important role in inhibiting pancreatic lipase and α-amylase. Its antioxidant properties could be responsible for its antidiabetic effect in rats **(Aierken *et al.*, 2017).**

Cardiovascular activity

Crataegus species are involved in many medicinal applications. Many researchers proved that *Crataegus* played an important role in improving many cardiovascular disorders like congestive heart failure, myocardial infarctions, and arrhythmia **(Kumar *et al.*, 2012)**. In US and Europe, hawthorn extracts were used as a treatment for patients with cardiovascular problems. The main species involved in heart and vascular system are *C. monogyna* and *C. laevigata* **(Liu, 2012)**. Shortness of breath and fatigue were recovered by hawthorn extracts, also, reducing symptoms of heart failure and improving heart function, these results were proved by meta-analysis from clinical trials including patients with heart failure taken a daily dosage of 160-1800 mg of the extracts. These studies showed that the extracts inhibit angiotensin converting enzymes (ACE) and alleviate production of angiotensin II in order to reduce blood pressure **(Kumar *et al.*, 2012)**. Moreover, the extracts exhibited a unique activity in comparison with cardiac drugs; it showed an anti-arrhythmic activity and treated myocardial infarction and myocardial ischemia. Hawthorn may be used as a coronarodilating agent, the infusing of the hydroalcoholic extracts of *C. meyeri* to rats decreased the number of ventricular beats. The infusing of 1 mg/kg/min of chloroform extract of *C. meyeri* to rats gave the same results **(Kumar *et al*., 2012**). In rats with aortic constriction and after treatment with hawthorn extract for three weeks, the systolic and diastolic dysfunction were alleviated **(Hwang *et al*., 2008**). Moreover, the hyperoside from *C. tanacetifolia* plays an important role in the structure of coronary arterial wall and blood pressure. It has beneficial effects on cardiovascular system, prevented L-NAME-induced hypertensive in rats **(Koçyõldõz *et al.*, 2006)**.

Table 3 Cardioprotective effect of hawthorn extract

Hawthorn (organ)	Concentration	Cardioprotective Effect	Reference
C. monogyna (Fruits) *C. laevigata* (Fruits)	160-1800 mg/kg	Inhibition of angiotensin converting enzymes (ACE) Alleviation of angiotensin II production Reduction of blood pressure.	**(Kumar *et al*., 2012)**
C. tanacetifolia (Leaves)	100 mg/kg	Prevention of L-NAME-induced hypertension.	**(Koçyõldõz *et al.*, 2006)**
C. oxycantha (Fruits)	0.5 mL/100 g bw/day	Prevention of isoproterenol-induced myocardial infarction. Inhibition of peroxidative injury of mitochondrial lipids.	**(Jayalakshmi *et al*., 2006)**

Anti-Cataract activity

Cataract is the driving cause of visual impairment around the world. It is a multifactorial illness primarily associated with oxidative stress delivered by free radicals. Both *in vitro* and *in vivo* approaches were attempted to investigate the anticataract potential of *Crataegus pinnatifida* extract. Using an *in vitro* approach, the leaves extract of *C. pinnatifida* inhibited the enzyme aldose reductase which disrupts the osmotic gradient that eventually will lead to the diffusion of water into the lens. At high levels, aldose reductase is responsible for the conversion of glucose into sorbitol. The inhibition of aldose reductase will prevent nerve and eye damage. Other *in vivo* approach reported that selenite-induced rats for oxidative stress when treated with *C. pinnatifida* leaves extract as eye drops for three times a day, the level of melondialdehyde (MDA) was significantly reduced and that of serum superoxide dismutase (SOD) was markedly increased in comparison with controls groups. The authors reported that the significant increase in the activity of the antioxidant enzymes explains the anticataract potential of the extract **(Kumar *et al*., 2012)**.

Anti-viral activity

The proanthocyanidin and flavonoid compounds of *C. aronia*, *C. pseudoheterophylla*, and *C. monogyna* leaves and berries exhibited a highly efficient capacity against herpes simplex virus. In addition, the trimeric procyanidin and flavonoids from *C. sinaca* exhibited an antiviral activity against HIV, by inhibiting the reverse transcriptase in the retrovirus (HIV) or by binding to the protein coat of the virus **(Kumar *et al*., 2012)**.

Table 4 Summary of the reported activities of Hawthorn extract. (CSE = Commercial standardized extract)

Hawthorn (organ)	Concentration	Health Effect	Model	Reference
C. laevigata (Berries) *C. pinnatifida* (Berries)	250 mg/kg	Hypolipidaemic	Rats	**(Rajendran *et al*., 1996)**
Hawthorn (CSE)	450 mg/kg	Hypolipidaemic	Human	**(Al-Gareeb, 2012)**
C. pinnatifida (Fruits)	250 mg/kg	Dyslipidemic	Mice	**(Niu *et al*., 2011)**
C. curvisepala (Flowers and Leaves) *C. tanacetifolia* (Leaves)	90- 100 mg/ml 100 mg/kg	Hypotensive	Human Rats	**Asgary *et al*., 2004;** **Kumar *et al*., 2012)**
Hawthorn (CSE)	1000 mg/kg 1500 mg/kg 2500 mg/kg	Hypotensive	Human	**(Asher *et al*., 2012)**
C. folium (Fruits) *C. pentagyna* (Fruits) *C. monogyna* (Fruits)	0.4 mg/mL	Antioxidant	HepG2 cells	**(Liu, 2012)**
C. pinnatifida (Fruits)	20 μM Oleanolic acid 40 μM Ursolic acid	Antioxidant Anti-inflammatory	PC12 cells	**(Tsai & Yin, 2008)**
C. pinnatifida (Fruits)	0.25-0.75 mg/ml	Anti-inflammatory	RAW 264.7 cells	**(Kao *et al*., 2005)**
C. pinnatifida (Fruits)	50-200 mg/ml	Anti-inflammatory	RAW 264.7 cells	**Li & Wang, 2011)**
C. aroni (fruits)	1200 mg/kg	Hypoglycemic	Rats	**(Aierken *et al*., 2017)**
C. oxycantha (Fruits)	0.51 mg/kg	Hypoglycemic	Human	**(Kadas *et al*., 2014)**
C. pinnatifida (Leaves)	160-900 mg/kg	Anti-Cataract	Rats	**(Kumar *et al*., 2012)**
C. sinaca (Fruits and leaves)	8.9 ug/ml	Anti-viral	T-cell model (MT-4 cells)	**(Kumar *et al*., 2012)**

CONCLUSION

The use of medicinal plants became prevalent and popular worldwide in treating many health conditions. *Crataegus* species exhibit a significant pharmacological activity due to presence of bioactive compounds including triterpenes, oligomeric procyanidins, epicatechin, and many other compounds. Numerous *in vivo* and *in vitro* studies on hawthorn point to its potential antioxidant, antidiabetic, hypotensive, antiviral, hypolipidaemic, and anticancer activities. The chemical composition and biomedical properties of *crataegus* may position this plant as a good candidate to be used in treating many different diseases.

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