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Perspective

Hawthorn (*Crataegus* spp.): An Updated Overview on Its Beneficial Properties

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Abstract: Medicinal plants, many of which are wild, have recently been under the spotlight worldwide due to growing requests for natural and sustainable eco-compatible remedies for pathological conditions with beneficial health effects that are able to support/supplement a daily diet or to support and/or replace conventional pharmacological therapy. The main requests for these products are: safety, minimum adverse unwanted effects, better efficacy, greater bioavailability, and lower cost when compared with synthetic medications available on the market. One of these popular herbs is hawthorn (*Crataegus* spp.), belonging to the *Rosaceae* family, with about 280 species present in Europe, North Africa, West Asia, and North America. Various parts of this herb, including the berries, flowers, and leaves, are rich in nutrients and beneficial bioactive compounds. Its chemical composition has been reported to have many health benefits, including medicinal and nutraceutical properties. Accordingly, the present review gives a snapshot of the in vitro and in vivo therapeutic potential of this herb on human health.

Keywords: hawthorn; bioactive compounds; *Crataegus*; biological activity; nutraceuticals; health benefits; plant extracts

1. Introduction

Medicinal wild plants and herbs have recently received increased interest worldwide since they are rich sources of bioactive compounds and for their potential beneficial health properties, which have often been well known for centuries [1–18]. The World Health Organization (WHO) reported that about 80% of the world's population uses traditional drugs, including herbal medicine, for the treatment of diseases before considering conventional drugs when available [19]. One of these interesting popular medicinal plants is hawthorn (*Crataegus* spp.), a deciduous branched shrub/small tree that is twisted and thorny, belonging to the *Rosaceae* family and *Maloideae* sub-family. Hawthorn is present worldwide with about 280 species, among which the most common are: *C. monogyna*, *C. laevigata*, *C. mexicana* and *C. douglasii*, grown in Europe, North Africa, West Asia, and North America. The scientific name of hawthorn comes from the Greek word "kràtaigos" which means "strength and robustness" due to its hard and durable wood. Natural habitats of hawthorn are wooded and sunny areas on predominantly limestone soils up to 1500 m above sea level. This species is very rustic and is not very water demanding. *C. monogyna* has leaves that are 20–60 mm long with a rhomboidal shape that are deeply engraved and have notched lobes; the flowers are white/pink and form blooms of 5–35 units; the fruits are red berries of 10 mm when ripened, and contain one seed. Flowering takes place between April and May, and fruit ripening between September and October. Various parts of this plant—in particular, the berries, flowers, and leaves—are rich in nutrients, and have been traditionally associated with many health, medicinal or nutraceutical beneficial health effects [20], e.g., anti-microbial, anti-inflammatory, antioxidant, anti-cancer, and anticoagulant properties. Some of the most relevant properties associated to this plant are reported in Figure 1. According to its traditional use, and since it is generally recognized as safe (GRAS), the Committee for Herbal Medicinal Products of the European Medicines Agency classified hawthorn as a "traditional herbal medicinal product" [21,22]. This wild plant has been used as a traditional medicine, herbal drug, and food supplement for centuries [23,24]. According to the holistic and traditional approach, hawthorn leaves and flowers are used to prepare infusions that can be used to control palpitations, tachycardia, and nervousness. Away from meals, hawthorn has been used against hypertension and, before sleeping, for its relaxing and sedative actions. The berries promote cardiovascular health, protecting from angina, hypertension, heart failure, cardiac arrhythmias, myocarditis, arteriosclerosis, insomnia, and anxiety. Moreover, the berries are astringents and diuretics, and can act against diarrhea, urinary retention, and intestinal cramps. Indigenous peoples from Latin America use the berries for the preparation of a highly energetic drink called "Pennican", and, in many parts of the world, the berries are used to prepare jams and as flavoring for dishes like white meats. Hawthorn, however, can also have a few collateral effects and contraindications; in particular, it is not recommended when blood pressure is low. Considering the multiple health properties of this medicinal wild herb, this review describes the potential use of hawthorn in therapy and as a support of some human health conditions.

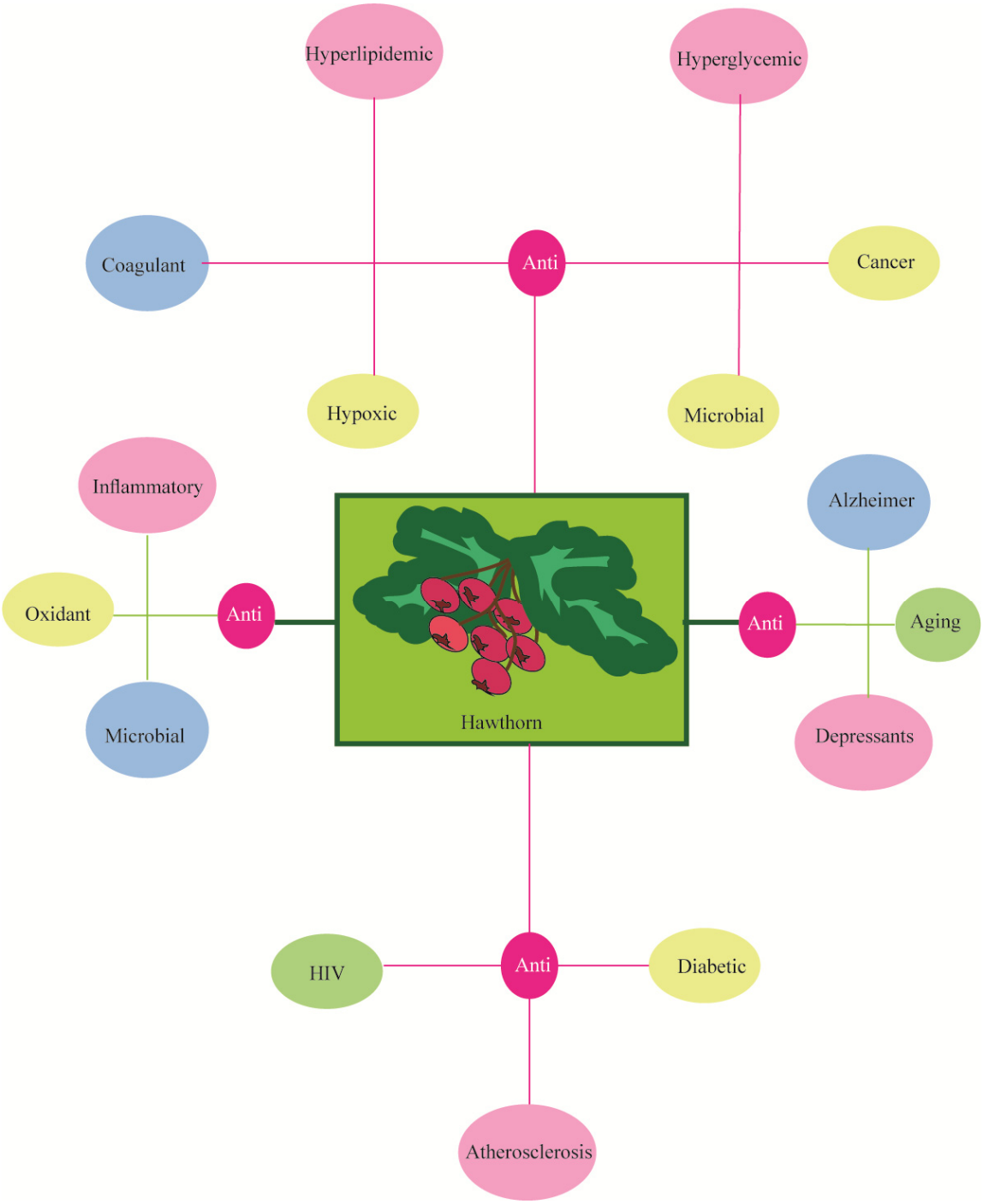

Figure 1. Scheme of the hawthorn therapeutic properties.

2. Phytochemical Composition of Hawthorn

Chemical analysis has allowed for the identification of more than 150 bioactive molecules in hawthorn, including phenolic acids (ferulic, gallic, p-coumaric, syringic, chlorogenic, caffeic), quercetin, pyrocatechin, phlorodizin, terpenoids, lignans, steroids, organic acids (fumaric, tartaric, succinic, citric, malic), and sugars (maltose, sucrose, glucose, fructose). These are represented in Figure 2 [25,26].

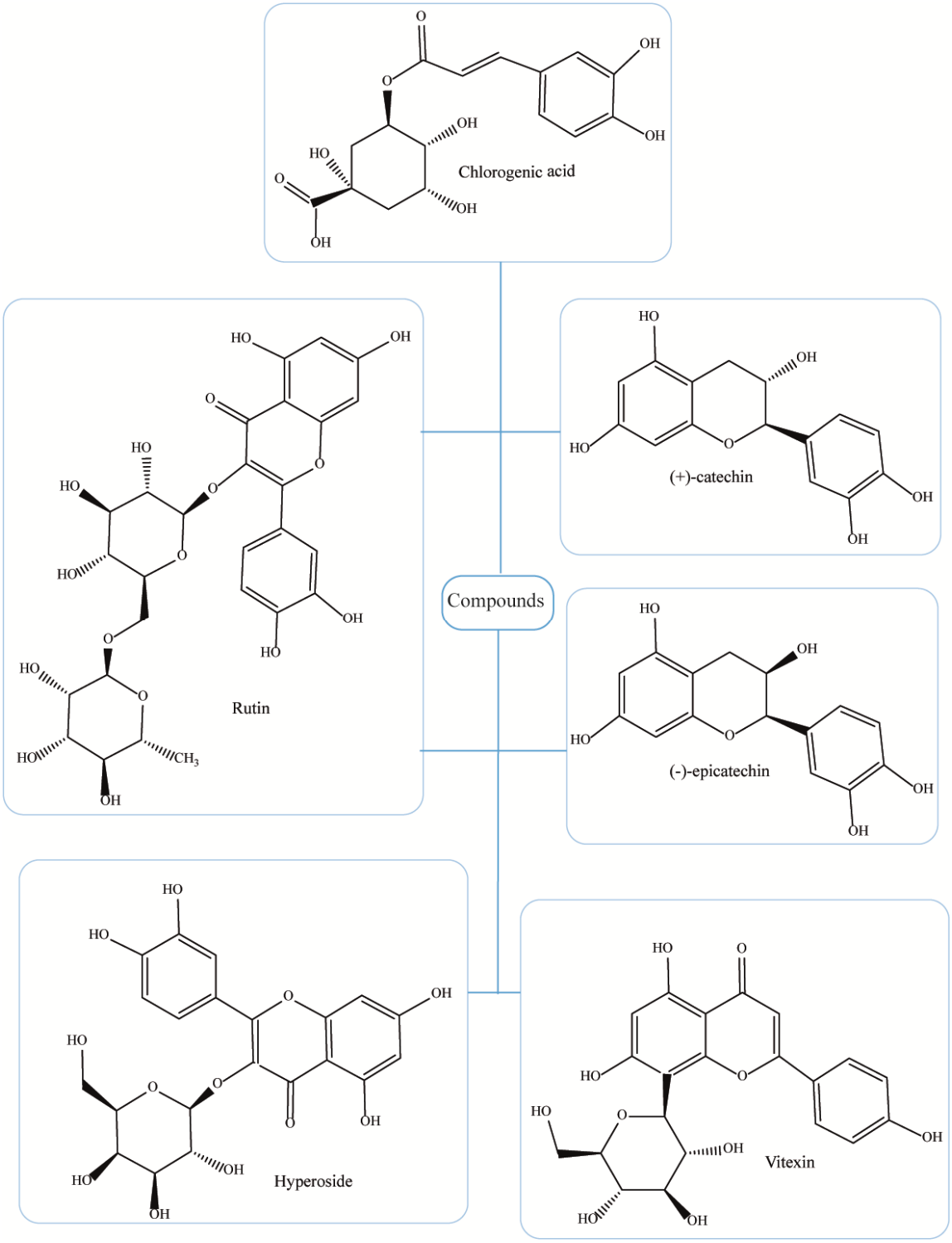

Figure 2. Overview of the main compounds found in hawthorn.

Polyphenol compounds from *C. oxyacantha* extracts, including epicatechin, epicatechin gallate (ECG), rutin, caffeic, and caftaric acids, were identified using HPLC-DAD and LC-MS/MS techniques [27]. In a study, UV/MS analysis coupled with 1D/2D nuclear magnetic resonance (NMR) spectroscopy was used to detect the compounds extracted from the ethyl acetate extract of *C. oxyacantha*, which included naringenin, epicatechin, quercetin-3-O-β-glucoside, and quercetin [28]. The presence of rutin and quercetin obtained from *C. oxyacantha* extracts using HPLC was also

reported [29]. The work of Nabavi et al. focused on the polyphenolic composition of *C. monogyna* Jacq., ranging from its chemistry and composition to its medical applications [30]. The recent work of Cao et al. [31] gives an updated snapshot of the water-based extraction of the bioactive principles of hawthorn, describing the current experimental laboratory research and further valuable information. In this study, attention has been addressed to the quantitative and qualitative aspects of the extraction, as well as to the kinetics of the extraction according to the part of the plant (flowers or leaves), their state (fresh or dried), and the granulometry of the dry plant, also taking into account parameters like stirring speed, temperature, extraction time, volume of the container (cup, mug or bowl) and the use of infusion bags. In agreement with green technologies [32,33], it is worth mentioning the work of Hu et al. [34], which proposed an eco-friendly microwave-assisted extraction of bioactive compounds from hawthorn leaf combined with ultra-high-performance liquid chromatography coupled with an ultraviolet detector for the identification and quantification of compounds. In a recent study, mannose, glucose and fructose were extracted from hawthorn fruits by acid hydrolysis using 2 M trifluoroacetic acid, and then identified and characterized by gas chromatography/mass spectrometry [35]. Zhao et al. [36] used headspace/solid phase microextraction (HS/SPME) coupled with gas chromatography/mass spectrometry (GC/MS) to determine the chemical composition of hawthorn fruits, reporting that alcohols and esters are the main compounds present. Salmanian et al. detected the phenolic acids contained in the hawthorn pulp and seed extract using RP-HPLC and reported that chlorogenic acid is the main one [37]. Liu et al. [38] applied HPLC-UV/ESI-MS to determine the phenolic constituents of hawthorn, which was found to contain C-glycosyl flavones, hyperoside, procyanidins B2/C1, and epicatechin. Lund et al. [39], by using nuclear magnetic resonance (NMR) spectrometry, identified chlorogenic acid and flavonoids of *Crataegus* species, including vitexin-2′′-O-rhamnoside, rutin, hyperoside, and naringenin. In their study, HPLC-DAD analysis was also used to confirm the obtained results. The hawthorn seed extract distillation at the optimum temperature (in the range of 211 to 230 °C) was analyzed by gas chromatography coupled with a mass spectrometer (GC-MS) to determine the chemical composition, with the aim of proposing this method as a cost-effective technique to obtain hawthorn products on an industrial scale [40]. The chemical compounds present in *Crataegus* species, mainly quercetin, hyperoside, rutin, and vitexin, have been also studied using HPLC-UV and UV-Vis spectrophotometry [41]. The hawthorn fruit examined by spectrophotometry at a wavelength of 285 ± 2 nm revealed the presence of hyperoside flavonoid in an amount up to 0.112–0.183% (*w*/*w*) [42]. Table 1 reports the main compounds found in hawthorn and the methodological and analytical approach used in their characterization.

Table 1. Identified compounds from hawthorn.

Species	Compound Identified	Methodological and Analytical Approach	Reference
Crataegus oxyacantha	Epicatechin, epicatechin gallate (ECG), rutin, cafeic and caftaric acids	HPLC-DAD and LC-MS/MS	[27]
Crataegus oxyacantha	Naringenin, epicatechin, quercetin-3-O-β-glucoside, and quercetin	Nuclear magnetic resonance (NMR) spectroscopy	[28]
Crataegus oxyacantha	Rutin and Quercetin	HPLC	[29]
Crataegus pinnatifida	Crataequinone A	Nuclear magnetic resonance (NMR) spectroscopy and electronic circular dichroism (ECD)	[43]
Crataegus songarica	Quercitin 3-O-galactoside and kaempherol-3-O-glucoside	HPLC-DAD-ESI/MS	[44]
Crataegus pinnatifida	Pinnatifidanin BVI	Nuclear magnetic resonance (NMR) spectroscopy	[45]

Table 1. *Cont.*

Species	Compound Identified	Methodological and Analytical Approach	Reference
Crataegus pinnatifida	Pinnatifidanoside F	Nuclear magnetic resonance (NMR) spectroscopy	[46]
Crataegus azarolus var	Quercetin 3-O-methyl ether, 3-β-O acetyl ursolic acid	Reversed phase HPLC (RP-HPLC)	[47]
Crataegus pinnatifida	(+)-(7S,8R)-crataegusin A and (−)-(7R,8S)-crataegusin A	Electronic circular dichroism (ECD)	[48]
Crataegus pinnatifida Bge	(−)-7S,8R-4,7,9,9′-tetrahydroxy-3,5,3′,5′-tetramethoxy-8-O-4′-neolignan	Electronic circular dichroism (ECD) and HPLC	[49]
Crataegus pubescens	(+)-catechin and (−)-epicatechin	Micellar electrokinetic chromatography (MEKC) and HPLC/UV	[50]
Crataegus pinnatifida	Chlorogenic acid (CA), vitexin-400-o-glucoside (VG), vitexin-200-o-rhamnoside (VR), orientoside (ORT), rutin (RT), vitexin (VIT) and hyperoside (HYP)	HPLC	[51]
Crataegus pinnatifida var. major N.E.Br.	(7′S, 8′R, 8R)-isolariciresinol-9′-β-D -glucopyranoside and lyoniside	Nuclear magnetic resonance (NMR) spectroscopy and LC-MS	[52]

3. In Vitro and In Vivo Therapeutic Potentials of Hawthorn: An Updated Snapshot

The evaluation of phytochemical composition can be considered as the first step for the determination of the beneficial health properties of a plant [53,54]. Figure 1 summarizes the health properties as reported in the literature from in vitro and in vivo studies.

As indicated above, many beneficial properties have been attributed to hawthorn, including anticancer [55], anti-HIV, anti-diabetic [56], and anticoagulant activity [57], cardioprotective effects [58–65], hepatoprotective effects, antihyperglycemic and antihyperlipidemic activities, wound healing effects [66], antimicrobial effects, gastroprotective effects, treatment of metabolic syndrome [67], regulation of cholesterol homeostasis [68], anti-atherosclerosis effects [69–72], anti-aging effects [73], ischemia protective effects [74], treatment of cognitive disorders, neuroprotective effects, regulating gastrointestinal motility [75], anti-inflammatory activities [76,77], regulation of the gut–brain axis [78], treatment of hypertension [79], antioxidant activity [80–85], anti-hypoxic activities [86], antidepressant effects [87], anti-Alzheimer's effects, and treatment of intestinal microbial disorder [88].

In the following sections, an updated snapshot of the various potential therapeutic effects of hawthorn in vitro and in vivo are described, as well as its beneficial properties for human health.

3.1. Health-Promoting Activities of Hawthorn In Vitro

Many in vitro studies reported different health-promoting effects for hawthorn extracts [89–92]. The administration of homogeneous polysaccharide (HPS) extracted from hawthorn at a concentration of 125–1000 μg/mL showed anticancer activity against a human colon cancer cell line HCT116, after 12 h by arresting the cell cycle and inducing cell apoptosis through extrinsic and intrinsic mechanisms using P38 mitogen-activated protein kinase and the phosphatidylinositol-3-kinase/AKT/mammalian target of rapamycin signaling pathway [93]. Hawthorn fruit peel extract exhibited antioxidant activity (2,2,1-diphenyl-1-picrylhydrazyl (DPPH) IC_{50} value of 6.72 μg/mL), acetylcholinesterase inhibitory effects (IC_{50} value of 11.72 μg/mL), and cytotoxic effects against the human tumor cells SKOV-3 and MCF-7 (IC_{50} values of 80.11 μg/mL and 2.76 μg/mL, respectively) [94]. A recent study concluded that hawthorn extract-Selenium nano particles caused mitochondrial dysfunction and intracellular

oxidative stress to start the apoptosis of HepG2 cells via the mitochondrial pathway [95]. Table 2 reports the results of the main in vitro studies.

Table 2. In vitro reported activities for hawthorn.

Experimental Conditions: In vitro		
Activity	**Effect**	**Reference**
Antimicrobial	Apigenin-7-O-glucoside and luteolin 3,7-diglucoside extracted from hawthorn were the most potent chemicals to eliminate *Ureaplasma urealyticum* with minimum inhibitory concentration value ranges of 0.48–3.9 μg/mL and 0.48–1.95 μg/mL, respectively.	[89]
Antioxidant and anti-inflammatory	Ursolic acid and oleanolic acid extracted from hawthorn showed anti-inflammatory and antioxidative effects in PC12 cells by decreasing the cell death induced by 1-methyl-4-phenylpyridinium ions (MPP+) and hydrogen peroxide (H_2O_2) as well as reducing lactate dehydrogenase leakage.	[90]
Anticancer	Crataequinone A exhibited cytotoxic effects on Hep3B and HepG2 cell lines with IC_{50} values of 24.90 μM and 12.24 μM, respectively.	[43]
Anticancer	Quercitin 3-O-galactoside and kaempherol-3-O-glucoside inhibited the culture of MCF-7 human breast cancer cells.	[44]
Anticancer	Pinnatifidanin BVI extracted from hawthorn had a preventive effect against Mrc5 human lung cells.	[45]
Antioxidant	Naturally occurring compounds from ethanolic and aqueous extracts of *C. monogyna* showed antioxidant and hydrogen peroxide scavenging properties.	[91]
Anti-inflammatory	Aqueous hawthorn fruit extract inhibited the expression of ILInterleukin-6, Interleukin-1β, Tumor necrosis factor-α and cyclooxygenase-2 genes, and prevented NO formation in RAW 264.7 cells.	[92]

The use of hawthorn induced anti-inflammatory properties through the modulation of lipopolysaccharide-induced pro-inflammatory (Interleukin-6 and Tumor necrosis factor-α) and anti-inflammatory (Interleukin-10) cytokines [96]. The flavonoids extracted from hawthorn could treat inflammatory bowel disease via the prevention of the nuclear factor kappa-light-chain-enhancer of activated B cells and extra cellular signal-regulated kinase 1/2 activity, the suppression of myosin light chain kinase and phosphorylatedmyosin light chain upregulation, the suppression of the production of inflammatory cytokines in Caco-2 cells, and the alleviation of inflammatory cytokine-induced intestinal barrier deficit [97].

The administration of *C. orientalis* berries and leaves at the concentration of 0.4 mg/mL displayed a DPPH radical scavenging effect and anti-inflammatory activity via the inhibition of 12- lipoxygenase (12-LOX) and cyclooxygenase-1 (COX-1), thereby impeding the generation of thromboxane B2 (up to 55.2%) and 12-Hydroxyheptadecatrienoic acid (up to 68.9%) [98]. In a study by Wyspianska et al., the procyanidins obtained from hawthorn bark extract revealed anti-inflammatory and antioxidant properties [99]. Furthermore, neolignans obtained from the ethanolic extract of hawthorn seeds exhibited anti-inflammatory and antioxidant properties, most likely due to the prevention of tumor necrosis factor-α) via the compounds 7′,8′-threo,7S,8R-1-[4-[(2-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-1-(hydroxymethyl)ethoxy]-3-methoxyphenyl]-1,2,3-propanetriol and 7′,8′-threo,7R, 8R-1-[4-[(2-hydroxy-2-(4-hydroxyl-3-methoxyphenyl)-1-(hydroxymethyl)ethoxy]-3-methoxyphenyl]-1,2,3-propanetriol, and the inhibition of NO production via leptolepisol D [100].

The antioxidant and anti-inflammatory bioassay-guided fractionation of the seed extract of mountain hawthorn, *C. pinnatifida*, led to the isolation of eight new lignans called hawthornnins, which showed different promising activities by scavenging free radicals and inhibiting TNF-α and NO production [101]. Zhao et al. observed α-glucosidase inhibitory and antioxidant activity for

C. pinnatifida fruit [102]. In another study, 8-O-4′ neolignans extracted from *C. pinnatifida* seeds blocked the activity of tyrosinase by 66.67%, in addition to exhibiting antioxidant activity [103]. Among the triterpenoids extracted from hawthorn berries, the compounds 3β,6β,18β,23-tetrahydroxy-olean-12-en-28-oic acid, 2α,3β,6β,18β-tetrahydroxy-olean-12-en-28-oic acid, and 2α,3β,6β,18β,23-pentahydroxy-olean-12-en-28-oic acid had antioxidant functions and could inhibit the proliferation of MCF-7 and HepG2 cells (EC_{50} = <5 μM) [104]. In a study by Chai et al. the proanthocyanidin compounds extracted from Chinese hawthorn fruits were characterized by HPLC-ESI-MS and MALDI-TOF-MS and examined for their bioactivities. The results showed anti-tyrosinase properties by preventing tyrosinases such as diphenolase and monophenolase and antioxidant activity [105].

Hawthorn seed extract at a concentration of 50 μM protected SH-SY5Y cells from damage through cell apoptosis prevention due to the presence of a sesquineolignan compound, 7′′,8′′-erythro;7R,8R,7′R,8′S)-3,7,3′,5′,3′′-pentamethoxy-4-hydroxy-4′,8-oxy-4′′,7′-epoxy-8′,5′′sesquineolignan -9,9′,7′′,8′′,9′′-pentanol, which was found to have a neuroprotective effect [106].

The extractions of *C. pinnatifida* fructus and *Rhodiolae kirliowii* radix and rhizome showed antiviral potential towards infection by the human polyomaviruses BK (BKPyV) and JC (JCPyV) by reducing the expression of viral proteins in the infected cells [107]. The growth of pathogenic *S. aureus* and *E. coli* was inhibited by gold and silver chloride nanoparticles functionalized by fruit extract of *C. pinnatifida*, which also scavenged DPPH free radicals and showed anti-inflammatory function via a reduction in the levels of inflammatory cytokines such as prostaglandin E2 (PGE2) and NO [108].

3.2. Health-Promoting Activities of Hawthorn in Animals

Many in vivo investigations have reported different beneficial functions for hawthorn [109–118]. The administration of hawthorn extract could attenuate atherosclerosis through the prevention of factors related to apoptosis and inflammation signaling pathways, by an apoptosis and inflammation resistance effect, vascular smooth muscle cells calcium deposition, lipidosis, preventing proliferation, lipid regulation, reducing interleukin-1β, hypersensitive C-reactive protein, monocyte chemoattractant protein-1, Bax mRNA expression and protein levels, as well as the enhancement of adiponectin level in serum and Bcl-2 (mRNA and protein expression) in the aorta [119]. In another study, the administration of hawthorn leaf flavonoids (20 mg/kg) to apo-lipoprotein E (apoE) knock-out mice for 16 weeks showed an improvement in atherosclerosis via the in vivo promotion of reverse cholesterol transport, the inhibition of foam cell synthesis, and the induction of antioxidant-related gene expression [120]. In a recent study, ethanolic hawthorn fruit extract in hypocholesterolemic rats exposed vascular protective activities due to the phenolic compounds with reactive oxygen species scavenging and cholesterol-lowering activities, resulting in high cholesterol intake and bile acid production via the upregulation of hepatic CYP7A1 mRNA expression [121]. The co-administration of resveratrol with hawthorn flavonoids following coronary artery bypass graft could decrease thrombotic restenosis and endothelial cell injury [122]. The cardioprotective role of hawthorn leaf extract in rats was attributed to some functions, including the enhancement of the antioxidant defense system, the improvement of heart antioxidant biomarkers, the elevation of inflammatory cytokine biomarkers, and the enhancement of serum parameters related to heart function [123]. Anti-inflammation and anti-oxidative stress effects for hawthorn leaf flavonoids through the suppression of PKC-α activation in rats with diabetes-induced cardiomyopathy has also been reported [124]. Alp et al. reported that *C. oxyacantha* alcoholic extract (40 μg/kg/min of digoxin) showed antiarrhythmic activity in rats [125]. The alcoholic extract of *C. oxyacantha* berries was given to rats with isoproterenol-induced myocardial infarction, and anti-apoptotic and anti-inflammatory functions were found as a result of reducing nitritive stress, lipid peroxidation and apoptotic processes [126]. Table 3 reports the main studies in animals.

Table 3. The main studies in animals involving hawthorn.

Experimental Conditions: In Animal Model		
Activity	**Effect**	**Reference**
Anticataract potential	*C. pinnatifida* leaf extracts used three times a day reduced the level of malondialdehyde and increased serum levels of catalase and superoxide dismutase in rats with selenite-induced cataracts.	[109]
Dyslipidemia therapy effect	*C. pinnatifi* fruit extract (250 mg/kg) for 7 days in high-fat-diet-fed mice with hyperlipidemia reduced blood lipid and lipid degradation by enhancing the hepatic expression of peroxisome proliferator-activated receptor α.	[110]
Anti- atherosclerosis effect	Oligomeric proanthocyanidins extracted from *C. oxyacantha* in Wistar rats decreased the differentiation of monocytes to macrophages via the downregulation of inflammation and the reduction of monocyte chemoattractant protein -1 and vascular cell adhesion molecule-1 levels.	[111]
Antibacterial effect	Hawthorn fruit extract (including monomers of (+)-catechin, (−)-epicatechin gallate and (−)-epigallocatechin) could control methicillin-resistant *Staphylococcus aureus* (MRSA) in septic mice by enhancing the accumulation of daunomycin inside MRSA cells and by downregulating the expression of *norA*, *norC* and *abcA* mRNAs (the main efflux pumps of MRSA).	[112]
Anti-inflammatory effect	The administration of *C. pinnatifida* dried fruit extract reduced the expression of hepatic cyclooxygenase-2 and nitric oxide synthase.	[113]
Radioprotective effect	The treatment of mouse bone marrow cells with phenolic compounds extracted from hawthorn (200 mg/kg) caused a reduction in 2-Gy γ-radiation-induced stress and genotoxicity.	[114]
Anti- atherosclerosis effect	The administration of sugar-free *C. pinnatifida* aqueous extract in atherosclerosis-induced rats resulted in the regulation of endothelial function and reduction of inflammatory responses and serum lipid levels.	[115]
Cardioprotective effect	The administration of aqueous extract of *C. tanacetifolia* leaf (100 mg/kg) for 4 weeks in rats prevented hypertension.	[116]
Cardioprotective effect	The administration of alcoholic extract of *C. oxycantha* (0.5 mL/100 g body weight/day) for a month prevented isoproterenol-induced myocardial infarction through a reduction in enzymes involved in the Krebs cycle. It also prevented peroxidative injury of mitochondrial lipids and preserved the mitochondrial antioxidant balance.	[117]
Analgesic and central nervous system activities	The administration of hawthorn seed and pulp extracts (1000 mg/kg) in mice reduced pain, sleep disorders, nervousness and stress with low toxicity.	[118]

A study reported anti-melanogenesis, antioxidant and antitumor roles for hawthorn extract. The treatment of tumor-implanted mice with total oligomer flavonoids from hawthorn extract (150 mg/kg body weight) for 21 days reduced the tumor weight and volume, prevented intracellular free radical scavenging activity, decreased the melanin production and blocked the tyrosinase in melanoma cells [127]. Yonekubo et al. observed that the use of different concentrations of *C. oxyacantha* fruit extracts for a week in mice induced genotoxicity activity [128].

The co-treatment of type I diabetes-induced rats by hawthorn extract (100 mg/kg per day), plus resistance training for five days/week for 10 consecutive weeks, improved memory and learning by decreasing lipid peroxidation and increasing total antioxidant capacity [129]. In another study, the administration of *C. oxyacantha* leaves (200 mg/kg and 400 mg/kg) improved memory and learning in rats with scopolamine-induced amnesia through the inhibition of dementia and oxidative damage [130]. Lee et al. observed that the administration of ethanol extract of *C. pinnatifida* fruits could treat Alzheimer's disease by inhibiting amyloid β accumulation [131].

The treatment of high-fat-diet-fed rats with *L. plantarum* grade A pasteurized milk ordinance -fermented hawthorn juice for 28 days showed hypolipidemic activity through the regulation of adipose tissues and liver morphology, the restoration of liver tissue and the reduction in low-density lipoprotein cholesterol, serum total cholesterol, lipid vacuolization and lipid metabolism levels [132]. The administration of *C. pinnatifida* with high-fat-diet-induced obese mice modulated the gut microbiota

activity by reducing serum triglyceride, decreasing fat and body weight, inhibiting adipogenesis and inflammation, and altering gut microbial abundance and diversity [133]. In a recent study, the use of different concentrations of HT048 (obtained from the extractions of *Citrus unshiu* peel plus *C. pinnatifida* leaves) in rats resulted in an anti-obesity effect after 12 weeks by dose-dependently suppressing the differentiation of adipocytes and the release of stimulated glycerol, reducing peroxisome proliferator-activated receptor-gamma and CCAAT/enhancer binding protein-alpha mRNA expression, decreasing body weight, lowering the serum lipid content, reducing hepatic lipogenesis-related gene expression and increasing β-oxidation-related gene expression, thereby indicating positive effects of HT048 to prevent obesity by blocking adipogenesis and lipogenesis [134].

Diabetic nephropathy was improved in rats treated with hawthorn leaf flavonoids through the improvement of renal function and the reduction of renal damage via a decrease in oxidative stress injury and the regulation of the p38/MAPK signaling pathway [135]. In another study, the methanolic extract of *C. oxyacantha* (100 mg/kg BW) in rats for 12 weeks treated hyperglycemia and dyslipidemia [136]. Aierken et al. treated rats with streptozotocin-induced type II diabetes mellitus with different concentrations of hawthorn extracts and reported hypoglycemic activity in the treatment animals via the elevation of pancreatic-released plasma insulin and by the reduction of total cholesterol, triglyceride and glucose levels in the blood [137].

Hawthorn showed hepatoprotective effects in rats with alcoholic liver damage via the reduction of LDL and total cholesterol levels, the regulation of serum lipids as triglycerides, the reduction of sinusoidal distension, congestion, necrosis, steatosis and fibrosis, as well as the reduction of cell damage markers (acid phosphatase, γ-glutamyltranspeptidase, alanine aminotransferase and aspartate aminotransferase). Furthermore, hawthorn exhibited antioxidant activity via the elimination of bilirubin, the regulation of glycogen levels in liver tissue, the elevation of serum total antioxidant capacity levels and the reduction of lipid peroxidation [138]. Li et al. [139] reported that the daily administration of flavonoids extracted from hawthorn leaf (50 mg/kg/day and 100 mg/kg/day) for three months reduced hepatic steatosis in rats with non-alcoholic fatty liver disease induced by a high fat diet due to the activation of the adiponectin/AMPK pathway. The use of hawthorn pectin pentaglaracturonide (150 mg/kg/day and 300 mg/kg/day) for 10 weeks in high-fat-diet-fed mice inhibited hepatic lipid accumulation and prevented hepatic fatty acid synthesis by reducing the gene expression of high-fat-diet-induced sterol regulatory element binding factor-1c, pyruvate kinase, acetyl-CoA carboxylase and fatty acid synthase [140].

In a study by Mustafa et al., the antioxidant activity and the immunomodulatory potential were seen for the hyperoside and ethyl acetate extractions of *C. azarolus* leaves on macrophages, cytotoxic T lymphocytes and natural killer cells [141]. Elango et al. [142] reported an immunomodulatory role for the ethanolic extract of hawthorn (100 mg/kg) in stroke rats over 15 days due to diminished brain apoptosis during reperfusion through the expression of Bcl-xL, the phosphorylation of signal transducer and activator of transcription 3, the elevation of the regulatory T cell (Treg) population and the prevention of activated inflammatory cells via increased levels of Foxp3-positive Tregs and IL-10, and reduced pro-inflammatory immune responses to ischemia and reperfusion-induced damage.

The daily use of hawthorn extract (100 mg/kg/day) for 11 days prevented alveolar bone loss in rats with periodontal disease via the regulation of oxidative stress, total oxidant and serum total antioxidant levels [143]. Others observed that the methanol extract of *C. dahurica* fruit caused an acceleration of the gastrointestinal tract and activation of the antioxidant system [144].

The polyphenol extract of hawthorn controlled the skin damage induced by UVB radiation via the suppression of p53, the reduction of DNA damage, the elimination of excess ROS, the downregulation of pro-apoptotic BAX and the upregulation of anti-apoptotic BCL-2, thereby preventing apoptosis and suppressing caspase-3/9 activation [145]. In another study, mice experienced the promotion of hair growth by taking *C. pinnatifida* extract through the induction of anagen phase, by mediating cellular signaling activation resulting in high proliferation and survival rate of human dermal papilla cells, as well as by increasing the Bcl-2/Bax ratio, resulting in protection from cell death [146]. Rats with

dehydroepiandrosterone-induced polycystic ovary syndrome experienced protective effects due to the consumption of hawthorn leaf flavonoids [147].

3.3. Health-Promoting Activities of Hawthorn Reported in Clinical Trials

Many clinical trials have reported different health-promoting activities for hawthorn [148–154]. In a study on 2681 patients suffering from congestive heart failure, the administration of hawthorn extract (900 mg/day) for 620 days reduced the odds ratio of sudden cardiac death in patients with lower left ventricular function [155]. Following the administration of hawthorn (450 mg, twice per day) for six months, 120 ambulatory patients suffering from symptomatic chronic heart showed no positive clinical effects in inflammation, oxidative stress, neurohormones, functional capacity and quality of life measures, but modest change in left ventricular ejection fraction was found [156]. Moeini et al. showed that 5 mL of hawthorn fruit extract after each meal in male and female patients with gastroesophageal reflux disease controlled the main symptoms over four weeks, as well as causing a 94.2% and 93.5% alleviation in regurgitation and heartburn, respectively [157]. According to the findings of Trexler et al. [158], 160 mg of hawthorn supplementation in adult subjects for a week could not influence electrocardiographic indices. In another study, adolescent subjects experienced hypertension following the supplementation of ethanolic extract of fresh *Crataegus* berries and natural D-camphor (Korodin®) [159]. Similarly, in a study by Erfurt et al. [160], sphygmomanometric blood pressure measurements before and after intervention confirmed the hypertension. In a recent clinical trial, a greater reduction was observed in the diastolic blood pressure in patients with type 2 diabetes over 16 weeks following daily consumption of 1200 mg of hawthorn extract [161]. Mildly hypertensive patients taking hawthorn extract (500–600 mg/day) over 10 weeks caused a decrease in both diastolic and systolic blood pressure [162]. The short-term use of camphor from *Crataegus* berry extract in women enhanced mental performance and blood pressure [163]. In Table 4, we list the reported examples of studies in humans involving hawthorn.

Table 4. Examples of studies in humans involving hawthorn.

Experimental Conditions: Clinical Trials			
Activity	**Administration**	**Main Findings**	**Reference**
Anti-inflammatory effect	Patients with diabetes (n = 37) received hawthorn vinegar (20 mL) diluted with water (40 mL) after meals for a month.	The treatment reduced serum levels of triglyceride, LDL, cholesterol and glucose, as well as decreased glycated hemoglobin, blood pressure and body weight.	[149]
Anti-hypertensive effect	Patients (n = 21) randomly received 1000 mg, 1500 mg and 2500 mg of hawthorn extract twice per day for four days.	The treatment lowered blood pressure.	[150]
Anti-hypertensive effect	Hypertensive patients (n = 60) received 450 mg of hawthorn extract twice per day for three months.	The treatment elevated the level of high-density lipoprotein and reduced the level of low-density lipoprotein, total cholesterol, diastolic blood pressure and systolic blood pressure.	[151]
Antihypertensive effect	The administration of hawthorn hydroalcoholic extract in subjects with primary mild hypertension.	A reduction in diastolic and systolic blood pressure after four months.	[152]
Treatment of patient with New York Heart Association class II heart failure	The administration of *Crataegus* berry extracts (30 drops, three times per day) in subjects with NYHA class II heart failure.	An improvement of confirmed tolerability and an enhancement of exercise tolerance after eight weeks.	[153]
Treatment of patient with New York Heart Association class II heart failure	The administration of *Crataegus* extract in subjects with congestive heart failure (NYHA class II).	A confirmation of the well-tolerated nature and safety of *Crataegus* extract based on in vitro parameters and treatment of congestive heart failure (NYHA class II) after 12 weeks.	[154]

4. Conclusions and Future Remarks

Medicinal herbs, including hawthorn, are rich sources of high market impact medicines around the world due to the presence of significant amounts of naturally occurring bioactive chemical compounds with therapeutic properties. However, further in vivo and in vitro research and clinical trials are needed to evaluate the link between the chemical compositions of such plants, particularly hawthorn, and their mechanisms of action in the treatment of various diseases. An emerging direction is suggested by the possible use of nanonutraceuticals, assuring their nutraceutical value at a nano level as well as safety and efficacy [164–168]. Nutraceutical science represents a great challenge for the future [169–172].

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