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Phytochemical composition and bioactivities of hawthorn (*Crataegus* spp.): review of recent research advances

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Abbreviations: ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid; AChE, acethylcholinesterase; AMP, adenosine monophosphate; BchE, butyrylcholinesterase; CPT-1, carnitine palmitoyl transferase; DPPH•, stable 2,2-diphenyl-1-picrylhydrazyl radical; DW, dry weight; eNOS, endothelial NO synthase; FRAP, ferric reducing antioxidant power; GAE, gallic acid equivalents; Gpx3, glutathione peroxidase 3; HDLC, high density lipoprotein cholesterol; HFD, high-fat diet; HLF, hawthorn leaf flavonoids; ICAM-1, intercellular adhesion molecule; IL, interleukin; LDLC, low density lipoprotein cholesterols; LPS, lipopolysaccharide; MDA, malondialdehyde; NAFLD, non-alcoholic fatty liver disease; NO, nitric oxide; ORAC, oxygen radical absorbance capacity; PKC-α, protein kinase C α; PPARα, peroxisome proliferator activated receptor α; RAW264.7, murine macrophage cell line; RCT, reverse cholesterol transport; ROS, reactive oxygen species; SOD, superoxide dismutase; SREBP-1c, sterol regulatory element binding protein-1c; TBARS, thiobarbituric acid reactive substances; TC, total cholesterol; TE, trolox equivalents; TFC, total flavonoid content; TG, triacylglycerols; TNF-α, necrosis factor-α; TPC, total phenolic content; VLDLC, very low density lipoprotein cholesterol.

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Abstract

Hawthorn (*Crataegus* spp.) is one of the most famous plants which has been used as natural medicine and nutraceutical. Its phytochemical composition, bioactive compounds and health benefits have been intensively studied and hawthorn preparations may be recognized as classical natural products for cardiovascular health. Polyphenolic compounds of different hawthorn anatomical parts as well as their extracts have been the focus of a majority of these studies, although various other classes of natural health promoting constituents have also been isolated, identified and characterized. Regardless, numerous published reports have particularly focused on the activity mechanisms which are very important for supporting various health benefits. This review summarizes the most recent studies on hawthorn, mainly published since 2015. Search of different databases indicates that approximately 200 publications, which are relevant to phytochemistry and health benefits of *Crataegus* spp., have appeared since then, most of them have not been included in the existing reviews.

Keywords: Hawthorn (*Crataegus* spp.); Phytochemical composition; Bioactivities; Health benefits; Toxicity.

1. Introduction

Hawthorns are large genus of small shrubs and trees belonging to Rosaceae family, Amygdaloideae subfamily, Maleae tribe, Malinae subtribe *Crataegus* Tourn. *ex* L. genus. Nowadays it is agreed that the genus is represented by approximately 200 species which are native to temperate regions of the Northern Hemisphere in North America, Europe and Asia (Phipps et al., 2003). The name "hawthorn" is often used in some countries although originally it was applied to the species native to northern Europe, especially to the common hawthorn (*C. monogyna*). Red or black small pome fruits of some *Crataegus* spp. are edible, e.g. fresh fruits of *C. orientalis*, while the fruits of other species

become eatable in late autumn. Their flavor has been compared to over-ripe apples and they are mainly used for jellies or home-made wine. Picked in spring young leaves are also edible and are tender enough to be used in salads. In Europe, the fruit, leaves, and flowers were traditionally employed for treating heart problems due to their antispasmodic, cardiotonic, hypotensive, and antiatherosclerotic effects. Nowadays, hawthorn preparations are mainly used as cardioprotective agents (Fong and Bauman, 2002); however, in traditional medicine it remains as a therapeutic agent for many other diseases including cancer, diabetes, cough, flu, asthma, stomach ache, rheumatic pain, nephritis, and hemorrhoids.

Among plant species *C. pinnatifida* (ten varieties of Chinese hawthorns) have long been used in traditional Chinese and European herbal medicines, and are widely consumed in the form of juice, drink, jam and canned fruit, while *C. monogyna* is commonly cultivated in the Mediterranean countries (Çalişkan, 2015). Chinese hawthorns comprise 18 species, however currently only *C. pinnatifida* and *C. pinnatifida* var. *major* fruits are included in the Chinese Pharmacopoeia. *C. pinnatifida* and *C. scabrifolia* fruits have also been traditionally used as peptic agents in oriental medicine and recently in a various local sweet foods, mainly soft drinks, jams, juices, tinned foods, and wines (Jurikova et al., 2012).

Several reviews summarizing numerous research findings on hawthorns are given in Table 1. Composition and health effects of phenolic compounds in *Crataegus* spp. of different origins was reviewed by Yang and Liu (2012), while Edwards et al. (2012) focused their review on the chemistry of the genus. Effects of bioactive natural products of *Crataegus* spp. on the vascular endothelium were also reviewed (Ahmad et al., 2013). More recently, polyphenolic composition and medical applications of *C. monogyna* were reviewed (Nabavi et al., 2015) by summarizing the growing evidence on various interesting physiological and pharmacological activities of this species due to the presence of different bioactive natural compounds. Nunes et al. (2017) reviewed the labeling and safety concerns of herbal products containing *Crataegus* spp. among other ingredients. Rastogi et al. (2016) provided a review on the cardiovascular effects of *C. oxyacantha*, including ischemic heart disease, congestive heart failure, arrhythmias and hypertension and concluded that, although the mechanisms of action are not very clear, there is enough evidence of their efficacy in various cardiovascular disorders.

C. oxyacantha is a widely used Chinese herb for treating gastrointestinal ailments and heart problems; it is also consumed as a food. In North America, the role of treating heart problems dates back to the 1800's. Currently, the evidence is accumulating from various *in vivo* and *in vitro* studies that hawthorn extracts exert a wide range of cardiovascular and pharmacological properties, including antioxidant activity, positive inotropic, anti-inflammatory, anticardiac remodeling, antiplatelet aggregation, vasodilating, and endothelial protective effects, as well as reduction of smooth muscle cell migration and proliferation, protection against ischemia/reperfusion injury, antiarrhythmic, lipid-lowering and arterial blood pressure decreasing effects (Wang et al., 2013).

Crataegus spp. were also reviewed together with other botanicals (Chen et al., 2009; Schmitt and Dirsch, 2009; Rastogi et al., 2016; Dennehy, 2001; Bjorklund et al., 2018), Chinese Traditional Medicine plants (Xie et al., 2012; Liu and Huang, 2016; Dong et al., 2017), various herbal products (Ahmad et al., 2013; Nunes et al., 2017), nutraceuticals (Houston, 2005) and natural antioxidants (Zhao, 2005).

2. Bioactive constituents and antioxidant/antiinflammatory activities

The variations in the composition of different *Crataegus* spp. from various growing regions, as well as of different anatomical parts of hawthorn have been widely studied. Acids, sugars and sugar alcohols, minerals, vitamins, and amino acid composition were among the analyzed constituents, however, overwhelming number of published articles have been focusing on polyphenolic compounds, as the most important hawthorn bioactive phytochemicals which may provide health benefits to humans. Consequently, many hawthorn-based preparations are standardized according to the content of their flavonoids and phenolic acids. The interest in phenolic and polyphenolic compounds particularly increased in the era of functional foods (Shahidi, 2004). Besides strong antioxidant activity, phenolic compounds have demonstrated numerous protective effects against chronic diseases, which have recently been reviewed (Shahidi and Yeo, 2018). This section will review only the most recent publications, which report new findings in the hawthorn phytochemistry. In general, the studies were performed for the isolation and purification of flavonoids, other groups of compounds, as well as determination of their variations among different origins and other variables.

Oxidative stress, which reflects an imbalance between the systemic manifestations of reactive oxygen species (ROS), may induce development of various diseases and disorders and, although living cells possess strong endogenous antioxidant system, it is believed that under some conditions ROS-protective function might be insufficient, while exogenous dietary antioxidants could assist in mitigating inflammatory processes and thereby restoring homeostatic state in the organism. In addition, natural antioxidants have attracted an increasing attention as possible alternatives to synthetic additives in foods and cosmetics. Hawthorns are well-known as an excellent source of natural antioxidants as reviewed in the literature (Venskutonis, 2016). The majority of such studies applied simple and easy spectrophotometric *in vitro* and *in situ* assays such as DPPH$^{\bullet}$ and ABTS$^{\bullet+}$ scavenging, FRAP, Folin-Ciocalteau's reaction (most often considered as TPC), ORAC, β-carotene-linoleic acid co-oxidation, TBARS and others. Although there is an opinion that such *in vitro* antioxidant capacity values are not appropriate, the experts in this area recently concluded that they, as low-cost and high-throughput tools, cannot be ignored (Granato et al., 2018). Therefore, together with phytochemical information this section will also briefly reviews the most recent findings in antioxidant properties of hawthorn products.

Phytochemical studies of the most widely used *C. pinnatifida* (Table 2) resulted in separation and purification of 4 new monoterpene glycosides and a new phenolic glycoside in addition to the 10 previously known ones (Li et al., 2015). Furthermore, 15 triterpenoids, including 4 novel acids, in hawthorn berries (Qiao et al., 2015); 2 norditerpenoids with unique carbon skeletons, 4 sesquiterpenoids and 9 nor-sesquiterpenoids from the ethanolic extract of plant leaves (Gao et al., 2017); 8 new phenylpropanoids (crataegusoids A-F) from the fruits (Guo et al., 2018); 8 new lignans (hawthornnins A-H) and 7 known analogues (Huang et al., 2015a); 2 new 8-*O*-4′-neolignans, huangnin A and B and four known analogs (Huang et al., 2015b); 7 new lignans (crataegusnins A-G) and 5 known compounds from the seeds (Peng et al., 2016) and from crude Crataegus Fructus drug (Kazuma et al., 2016), while 7 known main constituents were separated from the flavonoid fraction of leaves using a combination of high-speed counter-current chromatography (HSCCC) coupled with pre-HPLC (Wen et al., 2017). Crataegusins A and B, new flavanocoumarins, also showed

Table 1. Published review articles on *Crataegus* spp. bioactive compounds, pharmacological and health effects and safety

Plants or their products	Topic	Summary of content	Reference
Standardized *Crataegus* extracts	Treatment of heart failure	Positive inotropic, chronotropic, dromotropic effects; negative bathmotropic effects; increases coronary and myocardial perfusion, lowers peripheral resistance, has antiarrhythmic and economizing action with respect to oxygen and energy consumption.	Loew, 1997
Extract from fresh hawthorn berries	Orthostatic hypotension	In combination with D-camphor exerts a significant effect that counteracts an orthostatic fall in blood pressure	Belz and Loew, 2003
Hawthorn extract	Clinical trials to treat chronic heart failure	A significant benefit from hawthorn extract as an adjunctive treatment for chronic heart failure	Pittler et al., 2003
Hawthorn	Cardiovascular disease	May induce anti-ischemia/reperfusion-injury, anti-arrhythmic, hypolipidemic and hypotensive effects, which may in part be due to the presence of antioxidant flavonoid components.	Chang et al., 2005
Hawthorn medicinal extracts (WS 1442, LI 132)	Heart failure	Improvement in patients with mild forms of heart failure, clinical symptoms, pressure-heart rate product, left ventricular ejection fraction; no evidence of a notable reduction in mortality or sudden death	Dahmer and Scott, 2010
Standardized extracts from hawthorn leaves and flowers	Preclinical and clinical studies mild chronic heart failure	Cardiotonic effects, cardio- and vasoprotective properties; may be employed in the prophylactic and therapeutic treatment of endothelial dysfunction, atherosclerosis, coronary heart disease, or prevention of restenosis/reocclusion following peripheral endo-vascular treatment.	Koch and Malek, 2011
C. oxyacantha	Cardiovascular disease prevention	A wide range of cardiovascular pharmacological properties: antioxidant activity, positive inotropic effect, anti-inflammatory effect, anticardiac remodeling effect, antiplatelet aggregation effect, vasodilating effect, endothelial protective effect, reduction of smooth muscle cell migration and proliferation, protective effect against ischemia/reperfusion injury, antiarrhythmic effect, lipid-lowering effect and decrease of arterial blood pressure effect	Wang et al., 2013
C. pinnatifida	Chemical constituents, pharmacology, potential applications	>150 compounds (flavonoids, triterpenoids, steroids, monoterpenoids, sesquiterpenoids, lignans, hydroxycinnamic acids, organic acids and nitrogen-containing) have been isolated and identified; broad pharmacological effects with low toxicity; wide applications in pharmacological therapy	Wu et al., 2014
The genus *Crataegus*	Chemical, pharmacological, health, uses aspects	Heart (cardiovascular disorders), central nervous system, immune system, eyes, reproductive system, liver, kidney etc; cytotoxic, gastroprotective, anti-inflammatory, anti-HIV and antimicrobial activities. Bioactive phytochemicals: oligomeric procyanidins, flavonoids, triterpenes, polysaccharides, catecholamines; traditional uses; the clinical trials and regulatory status.	Kumar et al., 2012
Crataegus spp. of different origins	Composition and health effects of phenolic compounds	Epicatechin, aglycons and glycosides of B-type oligomeric procyanidins and flavonols, phenolic acids and C-glycosyl flavones as he major groups of phenolics; in vitro and animal studies showing cardioprotective, hypolipidaemic, hypotensive, antioxidant, radical-scavenging and anti-inflammatory potentials	Yang and Liu, 2012

Table 1. Published review articles on *Crataegus* spp. bioactive compounds, pharmacological and health effects and safety - *(continued)*

Plants or their products	Topic	Summary of content	Reference
C. oxycantha	Treatment of atrial fibrillation	Mechanisms of cardiovascular health benefits; lack of clinical studies evaluating its use in atrial fibrillation	Kanman-thareddy et al., 2015
C. monogyna Jacq.	Polyphenolic composition and medical applications	A critical review about physiological and pharmacological activities due to the presence of different bioactive natural compounds. In addition, scientific evidence suggests that the toxicity of hawthorn is negligible	Nabavi et al., 2015
Hawthorn juice	Various aspects	Nutritional characteristics, bioactives and antioxidant efficacy, phenolics, health effects, novel products/formulations and future trends	Venskutonis, 2016
Crataegus extract WS 1442	Benefit-risk assessment	Positive inotropic and antiarrhythmic properties; protecting from ischemic damage, reperfusion injury, and hypertension-related hypertrophy; improving endothelial functions (NO synthesis, delay of endothelial senescence); favorable safety profile (monotherapy and as add-on therapy); no drug interactions; no specific adverse reactions	Holubarsch et al., 2018
WS 1442 extract from *Crataegus* spp. leaves and flowers with 18.75% oligomeric procyanidins	Effects on cardiovascular system in vitro and in vivo, inc. large clinical trials	Beneficial cardioprotective values; free radicals scavenger; protect the ischemic heart tissue from neutrophile elastase action successions; vasorelaxant activity, via affecting eNOS synthase, and prevents ischemic heart tissue swelling by influence on calcium signaling pathways, and thus detain hyperpermeability of endothelium.	Zorniak et al., 2017
Crataegus spp.	Phenolic compounds; their bioactivity	Beneficial effects and the mechanisms of action involved are analyzed in a critical and systematic way in order to promote its use in the treatment of various diseases considered in Mexico as public health problems.	Cervantes-Paz et al., 2018
C. meyeri and *C. pontica*	Antioxidant properties and medicinal uses	The advantages of using natural remedies over their synthetic equivalents, the necessity of thorough investigations of less studied *Crataegus* spp	Dolatkhani and Jameie, 2015

a significant DPPH$^{\bullet}$ reducing activity compared with epicatechin (Kazuma et al., 2016). Most of the compounds isolated from the 70% ethanolic extract of *C. pinnatifida* seeds showed moderate DPPH$^{\bullet}$ scavenging activity and significant activities in the FRAP and ABTS assays. Furthermore, 6 compounds exhibited marked NO inhibition, 4 of them had a potent TNF-α inhibitory effect indicating that hawthorn seeds can be regarded as a potential new and cheap source of antioxidants and inflammation inhibitors (Peng et al., 2016). From *C. pinnatifida,* the isolated lignans demonstrated DPPH$^{\bullet}$/ABTS$^{\bullet+}$ scavenging efficacy, while some of them had anti-inflammatory activities, which was assessed by detecting the NO and TNF-α production in the LPS-induced RAW264.7 cells (Huang et al., 2015a). The fractions isolated with different polarity solvents from the crude 70% aqueous acetone extract of wood and bark of *C. pinnatifida* demonstrated antioxidative and anti-inflammatory activities. Thus, the n-butanol and ethyl acetate fractions of wood and bark, respectively, exhibited the strongest antioxidant effects, while all moisture-free fractions of wood showed high inhibitory effect on NO production (Bae and Kim, 2017).

Seasonal variations (May–October) in the yield of 7 phenolic compounds, the TPC in *C. pinnatifida* leaves, roots, twigs, and fruits were positively correlated with the temperature and length of daytime, while most remarkable radical scavenging and reducing power was determined for the leaves harvested in September (Luo et al., 2016).

Several articles have reported phytochemical studies of *C. azarolus* (Table 2). Thus, ethanolic extract of *C. azarolus* var. *eu-azarolus* Maire leaves was fractionated with different solvents and it was found that ethanol extract (70%) showed the highest DPPH$^{\bullet}$ scavenging activity compared to methanol, ethyl acetate and acetone extracts (Abu-Gharbieh and Shehab, 2017). A new ursane-type triterpene acid, named azarolic acid, and 8 known compounds were isolated from the crude ethyl acetate extract of *C. azarolus* var. *aronia* (Mahmud et al., 2016). Phytochemical composition of 20 phenolic compounds quantified in *C. azarolus* and *C. monogyna* fruits were compared (Mraihi et al., 2015). Methanol and ethanol extracts of *C. azarolus* exerted substantial antioxidant, anti-inflammatory, and antiproliferative capacities, which were evaluated by measuring the secreted amounts of the proinflammatory mediator prostaglandin E2 (PGE2), and by assaying the mRNA levels of the proinflammatory cytokines (IL-α, IL-β, and Il-6), chemokines (CCL3 and CCL4) and inflammation-sensitive COX2 and iNOS enzymes (Kallassy et al., 2017).

Dibenzo-*p*-furan derivatives and ursolic acid were isolated from

Table 2. Phytoconstituents of *Crataegus* spp. (recently reported; newly identified compounds are in italics)

Sample information	Name	Bioactivities, other study objective	Reference
C. pinnatifida, extract of leaves	4 monoterpene glycosides, *pinnatifidanosides A-D*; *phenolic glycoside*, *pinnatifidanoside E*; byzantionoside B, (3S,5R,6R,7E,9R)-3,6-epoxy-7-megastigmen-5, 9-diol-9-*O*-β-D-glcp, (65,7Z,9R)-roseoside, icariside B6, linalool oxide β-D-glc, shanyenoside A, dihydrocharcone-2′-β-D-glc, eriodectyol, vitexin, 2″-*O*-rhamnosyl vitexin	Antithrombotic effects	Li et al., 2015
C. pinnatifida, ethanolic extract of leaves	*Norhawthornoids A, B*; sesquiterpenoids shnyegenin B, shnyeside B, (3S,5R,6R,7E,9S)-megastiman-7-ene-3,5,6,9-tetrol, euodionosides D, (6R,9R)-3-oxo-α-ionol-9-O-β-D-glucopyranoside, (6S,7E,9R)-6,9-dihydroxy-4,7-megastiymadien-3-one-9-O-[β-D-xylopyranosy-β-D-glucopyranoside], linarionosides A, B, C; 3,9-dihydroxy-5-megastigmen-3-O-[β-D-xylopyranosy-β-D-glucopyranoside], pinnatifidanosides C, F, G.	Antithrombotic effects	Gao et al., 2017
C. pinnatifida, hydroethanolic extract of fruits	Crataegusoids: A(−), B, C, D, E (−) and (+), F	Cytotoxicity against cancer cells	Guo et al., 2018
C. pinnatifida, extract of seeds	8 new lignans, *hawthornnins A-H* and 7 known analogues	Antioxidant and anti-inflammatory	Huang et al., 2015a
C. pinnatifida, extract of seeds	2 new *8-0-4′ neolignans, huangnin A and B*; 4 known analogs	Tyrosinase inhibition	Huang et al., 2015b
C. pinnatifida, 70% ethanol extract of seeds	7 Crataegusnins A-G; 3 substituted propanetriols (3); leptolepisol D	Antioxidant and anti-inflammatory	Peng et al., 2016
Crataegus spp., 70% ethanol extract from seeds	*(7R, 8R, 8S)-,* (7′*S*, 8′*R*, 8*R*)-, (7′*R*, 8′*S*, 8*S*)-isolariciresinols, (7′*S*, 8′*R*, 8*R*)-lyoniresinol, (7′*S*, 8′*R*, 8*R*)-isolariciresinol-9′-*β-D*-glc, lyoniside, nudiposide	Inhibition of amyloid $A_{\beta 1}$–42 aggregation	Huang et al., 2018b
C. pinnatifida, flavonoid extract of leaves	(-)-Epicatechin, quercetin-3-*O*-(2,6-di-α-L-rhamnopyranosyl)-β-D-galactopyranoside, 4″-*O*-glucosyl and 2″-*O*-rhamnosylvitexins, vitexin, hyperoside and isoquercitrin	Isolation and purification of flavonoids	Wen et al., 2017b
C. pinnatifida var. *major*, crude Crataegus Fructus drug	*Crataegusins A and B* (2) (new flavanocoumarins)	DPPH reducing activity	Kazuma et al., 2016
C. azarolus var. *eu-azarolus* Maire, ethanol extract of leaves and its fractions	EtOH: rutin, salicylic and ellagic acids; chloroform and n-butanol fractions: ursolic, 3-β-O-acetyl ursolic, and ellagic acids, quercetin-3-O-β methyl ether, rutin and apigenin7-O-rutinoside	Anti-hyperglycemic activity	Abu-Gharbieh Shehab, 2017
C. azarolus var. *aronia*, ethyl acetate extract of leaves	A new ursane-type triterpene acid, *azarolic acid*, 4 known phenolic compounds; 4 known triterpene acids	Anti-vasoconstriction	Mahmud et al., 2016
C. monogyna, C. azarolus fruit	3 hydroxycinnamic and 1 hydroxybenzoic acid, 6 glucosylated flavonols and 2 flavones, 2 cyanidin glycosides; (-)-epicatechin, a dimer B2, two trimers, C1 and C2.	Phytochemical characterization	Mraihi et al., 2015
C. pycnoloba, total extract	4 dibenzofurans inc. newly discovered compound *6-hydroxy-2,3,4-trimethoxydibenzofuran*; ursolic aldehyde.	Melanin synthesis inhibition	Agalou et al., 2018
C. oxyacantha, shade dried plant twigs	*2-(3, 4-dimethoxyphenyl)-2-methoxyethanol, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl propan-1-one*, β-sitosterol-3-*O*-β-D-glc, lupeol, β-sitosterol, betulin, betulinic and oleanolic acids, chrysin (9);	Inhibition of acetyl and butyryl-cholinesterases	Ali, et al., 2017
Crataegus spp. from Bosnia, leaves with flowers, and berries	In mg/g DW: gallic acid (0.001–0.082), chlorogenic acid (0.19–8.70, rutin (0.03 to 13.49).	Phytochemical characterization	Čulum et al., 2018

Table 2. Phytoconstituents of *Crataegus* spp. (recently reported; newly identified compounds are underlined) - *(continued)*

Sample information	Name	Bioactivities, other study objective	Reference
C. pubescens, Fruit pulp (from Mexico)	In mg/100 mg DW: (+)-catechin (9.17±0.20), (-)-epicatechin (4.32±0.11), chlorogenic acid (5.60±0.24 mg/100); total proanthocyanidins 84.6±1.4 mg cyanidin; total flavonoids 55.89±1.43 mg quercetin.	Phytochemical characterization	González-Jiménez et al., 2018
C. microphylla Koch. ssp. *malyana* K. I. Chr. & Janjic, extracts of leaves with flowers	In mg/g DW: gallic acid 0.04, caffeic acid0.60, and hyperoside 2.61; TPC: 2.47 to 13.35 GAE; TFC: 0.01–1.09 QE	Phytochemical characterization	Čopra-Janićijević et al., 2018
Various *Crataegus* spp., flowers and leaves of 56 samples from Iran	TPC: 7.21–87.73 mg GAE/g DW; TFC: 2.27–17.40 mg/g DW; chlorogenic acid, vitexin-2-O-rhamnoside, vitexin, rutin, hyperoside, quercetin, isoquercetin	Flavonoids profile, antioxidant activity	Alirezalu et al., 2018
C. almaatensis Pojark, leaves, flowers and fruits	22 secondary metabolites (flavonoids and phenolic acids); TPC: 218 mg/g	Copmparison with *C. oxyacantha*	Bekbolatova et al., 2018
C. pinnatifida, commercial berries	15 triterpenoids, inc. 4 novel hydroxy-olean-12-en-28-oic (HOA) acids: 3-β,6 β,18 β-triHOA, 3 β,6 β,18 β,23-tetra HOA, 2 α,3 β,6 β,18 β-HOA, 2 α,3 β,6 β,18 β,23-pentaHOA	Antiproliferative and antioxidant activity	Qiao et al., 2015
Fruits, methanol, ethanol, acetone (80%) water extracts	Water (mg/g): vanillic (0.093), gallic (0.279) acids, catechin (3.622), chlorogenic (1.457 0.058) and ferulic (6.909) acid; acetone: epicatechin (2.71), protocatechuic acid (5.827)	Effect of solvents, antioxidant, α-glucosidase inhibitory activity	Miao et al., 2016
Crataegus spp., of leaves and flowers	81 components: benzaldehyde (82.54%) butyraldehyde (38.27%), (E)2-hexenal (21.67%)	Volatile, components, aroma	Ozderin et al., 2016
C. pinnatifida,	GC area %: Methyl acetate (4.40), n-hexane (2.90), 2-methyl-furan (1.80), 3-methyl-butyraldehyde (3.64), hexanal (2.08), furaldehyde (5.77), D-limonene (7.99)	Volatile compounds, aroma	Zhong et al., 2015
Hawthorn, pharmaceutical forms of inflorescence	Essential oil (%): 0.05 to 0.20% v/w; tricosane (12–17), (11–16), (6–11), *n*-hexadecanoic acid (1–11), nonadecane (3–7), (*E*,*E*)-α-farnesene (1–5), caryophyllene oxide (1–4), methyl eugenol (up to 6).	Essential oil, aroma	Kowalski et al., 2018

Abbreviations are: glcp,glucopyranoside; glc, glucoside; TPC,total phenolic content; TFC,total flavonoid content; GAE,gallic acid equivalents; and QE,quercetin equivalents.

C. pycnoloba extract, including the atom numbering of the newly discovered compound (Agalou et al., 2018); 9 compounds were isolated from *C. oxyacantha*, including 2 new natural products (Ali et al., 2017). Selected phytochemicals and antioxidant potential were studied in the *C. monogyna* ethanolic extracts from bark, leaves and berries: the highest TPC, radical scavenging potency as well as the levels of oleanolic acid, quercetin and lupeol were found in the bark extract, while the highest ursolic acid content was in the berries extract (Rezaei-Golmisheh et al., 2015).

The main phenolics in ethanolic extracts of leaves and berries of *C. orientalis* Pall. *ex* M. Bieb. from F.Y.R. Macedonia were hyperoside, isoquercitrin and chlorogenic acid (Šavikin et al., 2017), while vitexin and hyperoside, commonly found in chemotaxonomic investigations of *Crataegus* spp., were not detected in dry leaves with flowers, and berries of *C. rhipidophylla* Gand., *C.* × *subsphaericea* Gand., and *C.* × *macrocarpa* Hegetschw grown in Bosnia (Čulum et al., 2018). The presence of polymeric polyphenols (procyanidin dimers, trimers, and tetramers) in *C. pubescens* fruit from Mexico was reported for the first time (González-Jiménez et al., 2018). The composition and antioxidant activity *in vitro* were reported for different extracts of *C. microphylla* Koch subsp. *malyana* K. I. Chr. and Janjic; interestingly, the Soxhlet extract of leaves with flowers was best in DPPH$^{\bullet}$ scavenging (IC_{50} = 0.78 mg/mL) while that of berries was stronger as $ABTS^{\bullet+}$ scavenger with IC_{50} of 0.39 mg/mL (Čopra-Janićijević et al., 2018). TPC in methanol extracts of *C. monogyna* from nine different locations in central Spain was in the range of 117.7–204.3 mg GAE/g extract, the amounts of chromatographically quantified flavonoids and phenolic acids was 23.3–143.3 mg/kg, while ORAC and IC_{50} of DPPH$^{\bullet}$ scavenging values were 1.32–2.76 mol TE/mg and 0.82–3.76 g/mL, respectively (Abuashwashi et al., 2016). TPC and DPPH$^{\bullet}$ scavenging activity as well as the contents of metals (Zn, Fe, Cu, Mn, Cd, Cr, and Pb) were reported in wild *C. oxyacantha* from Serbia (Veličković et al., 2016).

Chlorogenic acid, hyperoside, and rutin were the most abundant phenolics in the extracts of hawthorn flowers in most genotypes of 56 studied *Crataegus* spp. samples collected from different geographical regions of Iran (Alirezalu et al., 2018). The composition of 22 secondary metabolites (flavonoids and phenolic acids) in leaves, flowers and fruits of endemic in Kazakhstan *C. almaatensis*

Pojark was compared with a well-known *C. oxyacantha* flowers. Leaf extracts were the richest sources of metabolites (TPC = 218 mg/g) and the most active DPPH$^{\bullet}$ scavengers (IC_{50} = 48 µg/mL), while the flowers of the Kazakh species were as rich in polyphenols as the *C. oxyacantha* (Bekbolatova et al., 2018).

Evaluation of 18 hawthorn genotypes selected from repository collection in Malatya province (Turkey) belonging to several *Crataegus* spp. revealed that the genotype 44MA12 (*C. monogyna* subsp. *azarella*) had the highest anthocyanin content (516 mg per 100 g fresh fruit) and the strongest DPPH$^{\bullet}$ scavenging capacity, while the genotype 44MA11 (*C. meyeri*) had the highest TPC, 3,460 mg GAE/100 g fresh fruit (Ercisli et al., 2015). Thirty-five compounds were isolated from *C. dahurica* methanol extract for the first time and their structures identified as triterpenoids and polyphenolics as the main components (Wang et al., 2018). Evaluation of antioxidant activities, TPC, TPF of crude methanolic extract and its fractions (ethyl acetate, diethyl ether, and chloroform) obtained from Algerian *C. azarolus* showed that the aerial parts extracts of this species are a good source of natural antioxidants (Lakache et al., 2016). Anthocyanin composition of different wild and cultivated berry species including Chinese hawthorn were quantified by Veberic et al. (2015). Thirty six compounds were reported in different extracts of hawthorn fruit, 15 of them were tentatively identified in hawthorn fruits for the first time (Miao et al., 2016). TPC, condensed tannin content and DPPH$^{\bullet}$/ABTS$^{\bullet+}$ scavenging capacities were higher for fruit extracts of *C. pinnatifida* Bge. var. *major* N. E. Br. (Shanlihong) than for the other two Chinese hawthorn varieties, namely *C. pinnatifida* Bge. (Shanzha) and *C. pinnatifida* Bge. var. *pinnatifida* (Dou et al., 2015). The advantages of Shanlihong variety, which exhibited elevated levels of TPC and TFC, including free and bond phenolics (procyanidin B-2 epicatechin, chlorogenic acid, hyperoside, and isoquercitrin), were also reported by Wen et al. (2015). Among the three tested varieties, the ORAC, and hydrophilic peroxyl radical scavenging capacity of the free faction were 398.3–555.8 µmol TE/g DW, and 299.1–370.9 µmol vitamin C equivalents/g DW, respectively, while the corresponding cellular antioxidant activity (CAA) values were 678–1,200 µmol of QE/100 g DW in the no PBS wash protocol, and 345.9–532.9 µmol of QE/100 g DW in the PBS wash protocol. Finally, the fruits of *C. pinnatifida* were subjected to *in vitro* digestion and it was determined that 37.41 and 31.51 mg GAE/g DW of TPC were released for Shanlihong and Dajinxing, respectively, while procyanidin B2, epicatechin, chlorogenic acid and catechin were the major released flavonoids. ORAC and peroxyl radical scavenging capacity well correlated with the released TPC or flavonoids (Zheng et al., 2018).

Some studies have reported the volatile compounds of hawthorn although the content of essential oil in *Crataegus* spp. is usually very low. For instance, in 4 tested pharmaceutical forms of hawthorn inflorescence it was from 0.05 to 0.20% (v/w) and composed mainly of long chain hydrocarbons (Kowalski et al., 2018). Zhong et al. (2015) identified 46 volatile compounds in *C. pinnatifida* with contents higher than 1% in the total GC area by HS-SPME coupled with GC-MS. The contents of furaldehyde, 5-methylfuraldehyde, methyl acetate, 2-methylbutyraldehyde, D-limonene and 2-methylfuraldehyde significantly changed after stir-frying and it might be important in odor changes. Volatile components were also reported in *C. pentagyna* subsp. *pentagyna*, *C. orientalis* subsp. *orientalis*, *C. orientalis* subsp. *szovitsii*, *C. tanacetifolia*, *C. azarolus* var. *aronia*, *C. monogyna* var. *lasiocarpa*, *C. monogyna* var. *monogyna* leaf and flower samples collected from different provinces of Western Anatolia (Ozderin et al., 2016).

The changes of phytochemicals during processing and storage were also studied. "Xinglongzirou" hawthorn wine bioactives and antioxidant capacity were determined during production and storage. Only six anthocyanins were detected after fermentation. Microwaving and heating pretreatments significantly increased the total amount of anthocyanin and antioxidant capacity values in the stored hawthorn wine while the TPC decreased (Liu et al., 2018). Heat and microwave pretreatments had also a significant impact on anthocyanins in hawthorn drink; more of them remained after heat treatment than after microwaving (0.745 mg/100 mL); these were 52.4% higher than those in the control group after storage for 7 days (Liu et al., 2016). Chemometric methods (spectrophotometry and HPLC) were successfully applied to differentiate raw and processed Crataegi Fructus (Fei et al., 2018). Significant differences in physicochemical characteristics associated with fruit quality and free amino acids were found during maturation of hawthorn fruits; for instance, the content of moisture, total soluble sugars, soluble pectin, reduced ascorbic acid, total ascorbic acid, fructose, and sucrose increased while crude protein content decreased significantly (Li et al., 2015).

Some studies were evaluating extraction methods. In general, selection of extraction solvents and procedures may have different goals, e.g. obtaining high total yields or recovery target bioactive fractions/constituents. Ethanol and water, as the most friendly and effective polar solvents, have been most widely used for food, natural pharmaceuticals and cosmetics. For instance, different ethanol concentrations (0–100%) were applied for *C. pinnatifida* and the yields were 19.03, 33.16, 27.79, 21.88, and 21.71% at 100, 70, 50, 30 and 0% (water) concentration, however the highest TPC and DPPH$^{\bullet}$/ABTS$^{\bullet+}$ scavenging capacity was obtained in case of 50% (Kang, 2015). The technical and economic advantages of pressurized hot water (90 °C) extraction of *C. monogyna* compared to traditional percolation with ethanol and water (70:30, v/v) was shown by successful incorporation of natural batch variability into the physico-chemical process modelling concept (Sixt and Strube, 2018). Matrix solid-phase dispersion process was also suggested as a good alternative to the classic methods for extracting polyphenols from *C. oxyacantha* fruits and leaves, although phenolic profile was solvent-dependent (Benabderrahmane et al., 2018). In addition, this study claimed that epicatechin gallate, caftaric acid and orientin were not previously reported in this species. Ultrasonic assisted extraction (UAE) using an alkyl polyglycoside surfactant and further separation and purification with commercial macroporous resins was shown as an effective techniques for recovery of vitexin and its 2″-*O*-rhamnoside from the leaves (Han et al., 2016a). The extract obtained by UAE from *C. pinnatifida* fruits demonstrated higher TPC, TFC and DPPH$^{\bullet}$ scavenging capacity (Park et al., 2017b). Aqueous solutions of citric acid and methanol were compared for *C. monogyna* fruit; it was found that the former was favorable in terms of total yield, TPC and ascorbic acid, while DPPH$^{\bullet}$ and ABTS$^{\bullet+}$ scavenging capacity was not dependent on the solvent (Pliszka et al., 2016). Hawthorn seeds, as a byproduct of manufacturing hawthorn juice and jam, were evaluated as a potential new and cheap source of antioxidants and inflammation inhibitor (Huang et al., 2015).

A protocol for preparative isolation of oligomeric and polymeric procyanidins from an acetone-water extract of Crataegi folium *cum fore* was developed, yielding procyanidin reference clusters with defined degree of polymerization (DP) from 2 to 10 (Hellenbrand et al., 2015). In addition, monitoring of procyanidin distribution during seasonal growth of fresh *C. monogyna* plants showed that their contents were between 20 and 55 mg/g DW of oligomeric procyanidins during the growing season in the different plant organs with strong accumulation in the flowers and fruits (55 mg/g DW). Regarding other components, the viscoelastic behavior and texture profile of gels, composed of the high methoxypectin in

hawthorn, were compared with commercial citrus gels (Linares-Garcia et al., 2015); the homogenous polyphenolic-polysaccharide conjugates (MW > 760 × 10^3 and 970 × 10^3 g/mol) containing some flavonoid units and rich in galacturonic acid with low esterification degree were isolated from flowers and fruits of *C. monogyna* (Pawlaczyk-Graja, 2018).

3. Cardioprotective benefits

Cardiovascular health benefits of various *Crataegus* drugs and other preparations have been most widely studied. In addition, the potential role of hawthorn in cardiovascular diseases was specifically reviewed by Chang et al. (2005). Hawthorn extracts have been used for this purpose in many countries, particularly against mild forms of chronic heart failure. For instance, search word combination *Crataegus*+cardiovascular in Clavirate Analytics Web of Science (WoS) since 1980 gave 286 records, and even during last 4 years (since 2015) the number of publications on this topic remains quite high, 61 (accessed on December 7, 2018). Consequently, the interest in hawthorn as a source of natural cardioprotective medicine, nutraceutical and functional food is evident.

Hawthorn extract WS 1442 containing a range of pharmacologically active substances including oligomeric proanthocyanidins and flavonoids is, possibly, the most famous *Crataegus* fruit-based drug with 89 and 14 records in WoS since 1980 and 2015, respectively. Moreover, two most recent articles reviewed WS 1442 in terms of experimental and clinical experiences (Zorniak et al., 2017) and benefit-risk assessment (Holubarsch et al., 2018). Therefore, only those studies, which were not reviewed in these publications, will be covered briefly. Thus, Fuchs et al. (2017) reported that WS 1442 protective effects against mild forms of chronic heart failure dysfunction may be due to the promotion of endothelial barrier integrity and inhibition of endothelial hyperpermeability, which are exerted by activating barrier enhancing (cortactin activation) and blocking barrier disruptive (calcium signaling) pathways, respectively. Bioactivity-guided fractionation of WS 1442 using successive elution with water, 95% ethanol, methanol, and 70% acetone, revealed that only the ethanolic fraction interfered with calcium signaling and only the methanolic fraction led to an activation of cortactin. Moreover, the role of phenolic compounds was excluded from the calcium active substance, whereas cortactin activation was attributed to oligomeric procyanidins with a distinct degree of polymerization (Fuchs et al., 2017). The study with human umbilical vein endothelial cells (HUVECs) exposed to TNF-α, with or without simvastatin (positive control) and WS 1442, suggested that the factors upregulating miR-155 expression, which decreases eNOS expression and endothelial function impairment, may be mitigated by WS 1442 (Wang et al., 2018). The results demonstrated that both TNF-α and WS 1442 increased miR-155 expression and decreased eNOS expression, however, unlike TNF-α, WS 1442 increased phosphorylated eNOS expression and NO concentrations and mitigated the overall negative effect of miR-155. Protecting effects of total flavones of hawthorn combined with resveratrol on the endothelial cells injury after artery bypass graft surgery were demonstrated in the study with rabbits, which determined that the level of circulating endothelial cells, density and the expressions of albumen and mRNA of ICAM-1 were significantly decreased (Zhu et al., 2018). It was also reported that WS (R) 1442 improved vascular function in diet-induced obese mice (Xia et al., 2016). The activity of WS 1442 in stimulating cardiomyocyte differentiation from murine and human embryonic stem cells (ESC) after forming mesoderm was validated in a mESC-based spontaneous differentiation assay, while bioassay-guided fractionation suggested that this activity is exerted by specific classes of compounds (Halver et al., 2015). Aerobic exercise and administration of *C. oxyacantha* extract reduced ICAM-1 and E-selectin in serum levels of 80 stable angina pectoris patients and such combined treatment was suggested as an effective complementary strategy for lowering the risk of atherosclerosis and heart problems (Jalaly et al., 2015).

The cardiac effects of hydroalcoholic extract of *C. pentagyna* leaf as well as isoquercetin and vitexin were studied using cardiomyocytes differentiated from healthy human embryonic stem cells, namely long QT syndrome type 2 and catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1) patient-specific induced pluripotent. It was concluded that tested preparations may be introduced as a novel nutraceutical with antiarrhythmic potential for CPVT1 patients (Pahlavan et al., 2018). The effects of polyphenolic extracts of *C. pentagyna* and *C. microphylla* fruits on hypoxia, which is a state of oxygen deficiency occurring in heart diseases, ischemia, bleeding and heart attack, were studied using male Swiss albino mice model. It was found that the extracts exhibited significant anti-hypoxic activity and prolonged animal survival time (Ebrahimzadeh et al., 2018). The activity of these extracts was attributed to a high TPC, 1,136.0 and 721.1 GAE mg/g in *C. pentagyna* and *C. microphylla*, respectively. Polyphenolic-polysaccharide conjugates from flowers and fruits of *C. monogyna* prolonged the plasma coagulation process in *in vitro* tests, even at a concentration of 31.25 μg/mL; however, only the product from flowers was highly selective in its action. It was mainly the indirect inhibitor of factor Xa, mediated by antithrombin, where such mechanism of activity is typical for highly sulfated glycosaminoglycans (Pawlaczyk-Graja, 2018).

Flavonoid-rich preparations of *C. pinnatifida* leaves (HLF) have been used to treat cardiovascular diseases; however, their ability to attenuate atherosclerosis development and possible mechanism are not evident. To fill this gap, Dong et al. (2017) by the large scope *in vivo* studies using apoE knockout mice showed that administration of HLF resulted in the following effects: (1) reduction of the mean atherosclerotic lesion area in *en face* aortas; (2) decrease in total cholesterol (TC) and very low density lipoprotein cholesterol plus low density lipoprotein cholesterol (VLDLc+LDLc) levels; (3) increase in PPARα mRNA and RCT; (4) decrease in SREBP-1c; (5) induction of CPT-1 mRNA, SOD1 and SOD2, Gpx3 mRNA, LDL receptor mRNA and protein levels; and (6) inhibition of the foam cell formation. HLF also protected rats against diabetic cardiomyopathy and the mechanism may be involved in reducing oxidative stress and inflammation *via* inactivation of the PKC-α signaling pathway (Min et al., 2017).

The new norditerpenoids (Table 2) isolated from the leaves of *C. pinnatifida* exhibited exceptionally potent antithrombotic activities *in vitro* and *in vivo*, pinnatifidanoside F being the most potent one (Gao et al., 2017). It inhibited ADP induced platelet aggregation, which is mediated through the response to the specific receptor of P2Y(12), and prolonged the time to form thrombocytes induced by $FeCl_3$ in the caudal vessels of zebrafish. *In vivo* study with diabetic rats demonstrated that resistance training and *C. oxyacantha* extract can synergistically decrease ischemia-reperfusion injury by oxidative stress reduction: injury indices (plasma lactate dehydrogenase, creatine kinase myocardial band isoenzyme and infarction size) were significantly lower after sedentary diabetic group treatment with extract, whereas glutathione peroxidase and myeloperoxidase levels after reperfusion increased and decreased, respectively, in response to training and *C. oxyacantha* (Ranjbar et al., 2018). On the other hand, the study with 116 patients who underwent cardiac surgery showed that those who recently consumed

hawthorn extract had a significantly higher rate of postoperative bleeding and overall mortality rate, which indicates that hawthorn extract consumption increases the potential for bleeding and the amount of chest tube output after cardiac surgery (Rababa'h et al., 2016).

C. oxyacantha alcoholic extract produced an antiarrhythmic effect that was induced by digoxin in Wistar rats; however, in the clinical use of this extract, the hypotensive effect should be considered (Alp et al., 2015). Another *in vivo* study reported that administration of methanolic *C. songarica* extract at the dose of 300 mg/kg body weight to albino rats with CCl_4-iduced toxicity significantly decreased serum creatinine, urea, and cholesterol, malondialdehyde (MDA) in kidney and heart tissues, along with recovery in antioxidant enzyme levels (Ganie et al., 2016). It was also reported that standardized *Crataegus* extract prevented DOCA-salt-induced hypertension and alteration of cardiac, vascular and renal structure and function in rats (Schini-Kerth et al., 2015). One of the main hawthorn bioactives vitexin inhibited cytochrome P450 enzyme (CYP3A1) in a concentration-dependent and time-dependent manner while CYP2C11 enzyme activity was induced after short period treatment but inhibited after long period treatment. It was concluded that vitexin can either inhibit or induce the activities of these enzymes and possible herb-drug interactions should be considered when vitexin is co-administered with some CYP2C11 or CYP3A1 substrates in clinic (Wang et al., 2015).

Some studies reported antithrombotic and anti-vasoconstriction effects exerted by *Crataegus* bioactives. Thus, among 15 from *C. pinnatifida* leaves isolated compounds (Table 2) (65,7Z,9R)-roseoside, eriodectyol and 2″-*O*-rhamnosyl vitexin exerted potent antithrombotic activity *in vitro*, which was in agreement with the *in vivo* results obtained in transgenic zebrafish system (Li et al., 2015). *C. monogyna* and *C. davisii* significantly inhibited the carrageenan-induced mouse tail thrombosis and may potentially be used as therapeutic agents or complementary treatments against thrombosis (Arslan et al., 2015). Euscaphic acid isolated from the crude ethyl acetate extract of *C. azarolus* var. *aronia* showed high anti-vasoconstriction effects on aortic rings, supporting the use of this medicinal plant in cardiovascular disease (Mahmud et al., 2016).

4. Hypolipidemic and hypoglycemic activity

4.1. Hypolipidemic effects

Lipid-lowering effects of hawthorn have been widely studied *in vivo* in many cases using HFD animals. Plant preparations demonstrated the ability to lower tricylglycerol (TG), total cholesterol (TC), LDLC and VLDLC, and to increase HDLC in plasma and these effects have been explained by several possible mechanisms (Yang and Liu, 2012). Recently published articles extended existing knowledge on hypolipidemic benefits of *Crataegus* preparations, particularly HLF, some of them carried out in *in vivo* studies with NAFLD animals and reported beneficial effects on liver health, which highly depends on HFD.

C. pinnatifida extract decreased the levels of serum TC, LDLC, hepatic TG and MDA, increased mRNA expression of nuclear erythroid 2-related factor (Nrf2), heme oxygenase-1 (HO-1), Gpx and reversed the suppression of protein levels in ovariectomized rats (Yoo et al., 2016). Li et al. (2015) reported that *C. pinnatifida* HLF ameliorated hepatic steatosis by enhancing the adiponectin/AMPK pathway in the liver of HFD-induced NAFLD rats. Several beneficial events were determined: (1) lowering body and liver weight and liver/body weight ratio; (2) improving serum parameters and liver dysfunction; (3) decreasing hepatic lipid accumulation; (4) increasing circulating adiponectin levels and up-regulating the expression of adiponectin receptors (AdipoR2) in the liver; and (5) activating AMP-activated protein kinase (AMPK) and altering AMPK-mediated SREBP-1c, PPAR-α and their downstream targets (Li et al., 2015). The inhibitory activities of *C. pinnatifida* extract isolated with 50% ethanol were more effective against formation of advanced glycation end products (AGEs) and α-glucosidase, while water extract better inhibited aldose reductase (Kang, 2015).

Investigation of the effects of aqueous extract of *C. aronia* (syn. *azarolus* L.) on sperm parameter and testicular structure in control and NAFLD-induced rats showed the improvements of the following indicators: (1) lower hepatic TG and cholesterol contents; (2) higher levels of testosterone, luteinizing hormone and follicle-stimulating hormone; (3) increased epididymis weight, sperm count and motility; and (4) increased testicular levels of glutathione, higher protein levels of Nrf2, γ-glutamylcysteine synthetase and SOD (Dallak, 2018).

The potential of novel multi-targeted herbal formula containing Crataegus Fructus, sylimarin, Schisandrae Fructus and *Momordica charantia*, as a therapeutic agent for diet-induced metabolic syndrome with special emphasis on NAFLD, dyslipidemia and type 2 diabetes, was studied using male C57Bl/6 mice. Crataegus Fructus aqueous extract inhibited differentiation of 3T3-L1 preadipocytes and cholesterol uptake into Caco-2 cells, while the whole herbal formula exhibited mitigation of diet-induced increase of various indicators *in vivo*, namely (1) a trend to reduce body weight and fat pad mass, (2) significant reduction in liver weight, liver lipid, and plasma lipid, (3) reduction of liver inflammation, and (4) improvement of adiponectin level (Elaine et al., 2018).

The results of a number of studies support the hypothesis that hawthorn possesses both therapeutic and protective effect for NAFLD. *C. aronia* extract and simvastatin significantly reduced lipids and thiobarbituric acid reactive substances (TBARS), which were increased by oxidative stress in HFD rat group, and treated damage to hepatic cells, while only the extract induced GSH. *C. aronia* and simvastatin treatments differentially reversed hepatic injuries (Al Humayed et al., 2017). Another *in vivo* study demonstrated that *C. aronia* significantly reduced liver index (3.85% versus 6.22% in HFD rat group), increased HDLC/LDLC and improved oxidative stress biomarker and enzymes indicating liver damage (Al Humayed, 2017). Ethanol extract of *C. oxyacantha* administered at 10 and 20 mg/kg to HFD rats reduced the level of some liver biomarkers, especially lactate dehydrogenase (LDH), increased GSH and FRAP and decreased lipid peroxidation, which may be beneficial in restoring the hepatocyte damage (Saeedi et al., 2018).

Polyphenols-enriched extracts from hawthorn fruit peels (HPP) and flesh (HFP), containing chlorogenic acid, epicatechin, rutin and hyperoside as the main polyphenolic constituents (HPP > HFP), reduced alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities, as well as the ratio of pro-apoptotic protein with B-cell lymphoma-2 (Bax/Bcl-2) in mice with liver injury, which was induced by a high-fructose diet. HPP was more effective than HFP in mitigating liver inflammation and oxidative stress by inhibiting inflammatory cytokine (TNF-α, IL-1 and IL-6) release, elevating antioxidant enzyme activities and PPARα expression, reducing Nrf-2 and antioxidant response element (ARE) expression in mice. HPP-treated mice also had lower levels of TC, TG, LDLC, VLDLC and apoprotein B (Apo-B), and higher levels of HDLC and Apo-A1 than HFP-treated mice due to reduced expression of fatty acid syn-

thetase (FAS) (Han et al., 2016b).

Hypolipidemic and antioxidant effects of aqueous and ethanolic extracts of *C. pinnatifida* fruits were compared in hyperlipidemia rats and obvious differences between extracts were observed, probably due to the existing differences in the content of phenols (Shao et al., 2016). Polyphenolic extracts of *C. azarolus* and *C. monogyna* leaves, fruit peel, and pulp, possessing antioxidant activity, protected against thermal-cholesterol degradation while pre-treatment with the extracts preserved liposomes and rat liver-homogenate from oxidative Cu^{2+} and Fe^{2+} induced damage (Belkhir et al., 2016). Synergic effects and potential mechanisms of action of *Astragalus* polysaccharides combined with *Crataegus* flavonoids were studied with diabetic mice. The mixture significantly reduced the fasting blood glucose, food and water intake and restored increased serum insulin levels and islet cell function; it also increased protein expression levels of pancreatic and duodenal homeobox-1 and phosphorylated AMPK in the pancreatic and liver tissue samples, respectively. The mixture significantly increased the mRNA expression levels of neurogenin 3 (v-maf musculoaponeurotic fibrosarcoma oncogene), protein A and insulin, and simultaneously decreased the expressions of IL6, TNF-α and chemokine (C-C motif) ligand 2 in the pancreatic islet cells of diabetic mice (Cui et al., 2016).

One of the most important *Crataegus* phytochemical, hyperoside, induced apoptosis in human hepatic stellate LX-2 cells and decreased the levels of α-smooth muscle actin (α-SMA), type I collagen, and intracellular ROS. Remarkably, hyperoside also inhibited the DNA-binding activity of the transcription factor NF-κB and altered expression levels of NF-κB-regulated genes related to apoptosis, including pro-apoptotic genes Bcl-Xs, DR4, Fas, and FasL and anti-apoptotic genes A20, c-IAP1, Bcl-X-L and RIP1. These results suggest that hyperoside may have potential as a therapeutic agent for the treatment of liver fibrosis (Wang et al., 2016).

4.2. Hypoglycemic effects

Enzyme inhibitory activity *in vitro* is a simple and widely used method for the preliminary evaluation of hypoglycemic effects. Comparison of hawthorn extracts prepared from plant fruit using 80% ethanol, 80% methanol, 80% acetone and pure water revealed that acetone extract had the highest α-glucosidase inhibitory activity while the highest $DPPH^{\bullet}$ scavenging capacity and FRAP was exhibited by the water extract. Polyphenols, triterpenoids, protocatechuic acid and epicatechin contributed to the α-glucosidase inhibitory activity, while flavonoids, polyphenols, vanillic acid, gallic acid, catechin and chlorogenic acid contributed to the antioxidant activity (Miao et al., 2016).

Antihyperglycemic (Male albino mice) and antihyperlipidemic (Sprague Dawley rats) activities of the ethanolic extract of *C. azarolus* var. *eu-azarolus* leaves and the isolated 3β-O acetyl ursolic acid were proved by significantly reduced mice blood glucose level in a time-and dose-dependent manner, while ethanolic extract significantly reduced LDLC, VLDLC, TC and TG and increased HDLC. In addition, ethanolic extract and 3β-O acetyl ursolic acid reduced the activity of pancreatic lipase *in vitro* (Abu-Gharbieh and Shehab, 2017). *C. aronia* significantly improved the oral glucose tolerance test, lowered plasma glucose, serum lipid levels and the hepatic glycogen content. In addition, it significantly lowered the levels of hepatic lipid peroxidation, TNF-α and IL-6, while the level of reduced glutathione (GSII) was enhanced and SOD activity was increased (Mostafa et al., 2018). Regarding the mechanism involved, it enhanced hepatic mRNA expression of the insulin receptor A isoform (IR-A) and glucose 6-phosphatase (G6Pase), while the expression of glucose transporter-2 (GLUT-2) and glycerol kinase (GK) mRNA was lowered. Consequently, *C. aronia* ameliorated type 2 diabetes mellitus by inhibiting hepatic glucose output. Out of six tested plants, ethanolic extract of *C. monogyna* leaves exhibited the best α-glucosidase inhibition activity with IC_{50} = 10.39 μg/mL, and was stronger inhibitor of α-amylase and α-glucosidase than its traditionally made with hot water tea (Sayin et al., 2018).

Complex herbal formulas with *Crataegus* have also been tested. The potential anti-obesity effects (inhibition of lipogenesis and adipogenesis) of HT048 (a combination of *C. pinnatifida* leaf and *Citrus unshiu* peel extracts) was investigated *in vitro* and *in vivo* using 3T3-L1 adipocytes and male Sprague Dawley rats, respectively (Lee et al., 2015). HT048 suppressed, dose-dependently, adipocyte differentiation and stimulated glycerol release and decreased the expressions of PPAR and C/EBP mRNA in adipocytes while in rats it significantly reduced the body and fat, as well as serum lipid levels, decreased expression of the hepatic lipogenesis-related genes and increased the expression of the oxidation-related genes (Lee et al., 2015). The effects were supported one year later when it was demonstrated that HT048 decreased body and total white adipose tissue weight and serum insulin levels in HFD-fed obese rats, whereas at the molecular level the supplement downregulated genes involved in lipogenesis, gluconeogenesis, and adipogenesis, and up-regulated β-oxidation genes. In addition, no interactions were observed between HT048 supplementation and orlistat drug, which was also used in the study (Lee et al., 2016). Orlistat and *C. monogyna* ethanolic extracts significantly lowered the hypercholesterolemia-increased serum level of hepatic enzymes and lipid peroxidation level in the hypercholesterolemia-induced oxidative stress in rats, protected from hepatic thiol depletion, and improved lipid profile and hepatic damages (Rezaei-Golmisheh et al., 2015). The results of Cheng et al. (2015) study with mice demonstrated that supplementation with a formula composed of *Rhizoma dioscorea*, *Lycium barbarum*, *Prunella vulgaris* and hawthorn may be a potent alternative as an anti-diabetic health-promoting diet. Finally, hawthorn pectin pentasaccharide (HPPS) was shown to be more effective than pectin (HP) and pectin hydrolyzates (HPH) in decreasing the body weight gain, liver weight, and plasma and hepatic TC of hamsters fed by high-cholesterol diets. However, the HP group had higher cholesterol excretion capacities than the HPH and HPPS groups by inhibiting cholesterol absorption in the diet (Zhu et al., 2015a). Thus, HPPS could be a promising anti-atherogenic dietary ingredient for the development of functional food to improve cholesterol metabolism.

5. Anticancer effects

The majority of studies evaluating anticarcinogenic properties of plant origin products are based on cell cytotoxicity and apoptosis assays, while *in vivo* studies, which provide more relevant physiologically information, are rather scarce. In addition, the mechanism of activity is very important issue in evaluating anticancer properties. Several recent studies, which were focusing on anticancer effects of *Crataegus* extracts, their fractions and purified compounds, are reviewed in this section.

Hawthorn's health benefits are mainly associated with the high contents of polyphenolics. *C. pinnatifida* var. *major* fruits, containing high amounts of flavonoids and triterpenoids, showed potent antiproliferative effect against human cancer cells lines (liver, Hep G2; breast, MCF-7 and MDA-MB-231); particularly strong activity was determined for triterpenoids-enriched fraction and its main

ingredient ursolic acid, which induced restriction point G1 arrest, downregulated proliferating cell nuclear antigen (PCNA), cyclin-dependent kinase (CDK4), and a protein Cyclin D1 (in humans encoded by the CCND1 gene) and upregulated cyclin-dependent kinase inhibitor 1p21(Waf1/Cip1) in MDA-MB-231 cells (Wen et al., 2017). In addition, the supplements induced MDA-MB-231 apoptosis *via* mitochondrial death pathway induced by caspase (9 and 3) activation.

The studies performed by Mustapha et al. (2015, 2016a, b, c) demonstrated various effects of *C. azarolus* ethyl acetate extract as well as isolated from it hyperoside and vitexin-2″-*O*-rhamnoside. The extract and vitexin rhamnoside exhibited anti-proliferative activity against B16F10 melanoma cells and the ability to reduce melanin content by inhibiting the tyrosinase activities (Mustapha et al., 2015); it also demonstrated significant cellular antioxidant capacity against the ROS in B16F10 and primary human keratinocyte cells (Mustapha et al., 2016b). In addition, total oligomeric flavonoids extract (150 mg/kg body weight, 21 days) significantly inhibited tumor growth volume and weight in Balb/c mice inoculated with B16F10 cells and therefore was suggested as a new candidate for skin care products (Mustapha et al., 2016b). The extract and hyperoside also exhibited an immunomodulatory effect by modulating macrophage lysosomal enzyme activity and NO release in mice and anti-inflammatory activity, which was concomitant with the cellular antioxidant effect against macrophages and solenocytes (Mustapha et al., 2016a). Extract-induced growth inhibitory effect in human colorectal cancer cell lines HCT-116 and HT-29 was associated with DNA fragmentation, sub-G1 peak, loss of mitochondrial potential, and poly (ADP-ribose) polymerase (PARP) cleavage. The extract also induced the cleavage of caspase-8 and had no effect on steady-state levels of total Bcl-2 protein, whereas Bax levels decreased significantly in a dose-dependent manner in both tested cell lines (Mustapha et al., 2016b). It may also be mentioned that in searching of relatively mild and safe tyrosinase inhibitors, one of six isolated from *C. pinnatifida* seeds 8-0-4′ neolignans, demonstrated promising tyrosinase-inhibiting and good antioxidant activities (Huang et al., 2015b).

Two other studies also investigated the effects of hyperoside. It was suggested as a candidate of concomitant treatment for leukemia due to the ability to potentiate As_2O_3-dependent apoptosis of HL-60 human acute myeloid leukemia cells by upregulating LC-II and inducing autophagy effects (Zhang et al., 2015). In addition, hyperoside inhibited Bcl-2-associated agonist of cell death BAD from phosphorylating, reactivated caspase-9, and increased cell cycle regulating protein p27 levels. In another study, hyperoside dose-dependently (0.5, 1, 2 mmol/L) increased the expression of LC3-II and autophagosome numbers in human non-small cell lung cancer cell line A549 cells; however, such effects in human bronchial epithelial cell line BEAS-2B cells were not observed. Moreover, hyperoside inhibited the phosphorylation of Akt, mTOR, p70S6K and 4E-BP1, but increased the phosphorylation of ERK1/2 in A549 cells (Fu et al., 2016).

The extract from hawthorn fruit peel (EPHF), rich in phenolic compounds, exhibited dose-dependent cytotoxicity on MCF-7 and SKOV-3 human tumor cell lines with the IC_{50} of 2.76 and 80.11 μg/mL, respectively (Wu et al., 2017). Polyphenolic extracts of *C. azarolus* and *C. monogyna* leaves, fruit peel, and pulp (0.24–4.8 mg/mL) were cytotoxic to cancer Caco-2 cells, at the same time being nontoxic for differentiated Caco-2 cells (Belkhir et al., 2016). Ethanolic extract of *C. microphylla* flowers and leaf buds demonstrated cytotoxic and antiproliferative activity against HeLa cell (IC_{50} = 0.871 mg/mL) and least cytotoxicity on normal human peripheral mononuclear cells (Bura et al., 2016). Methanol, ethanol and ethyl acetate extracts of *C. songarica* K. Koch exhibited potent *in vitro* anticancer activity on MCF-7, HeLa, HepG2, SF-295, SW480 and IMR-32 cancer cell lines with IC_{50} values of 28.57–85.106 μg/mL, while methanol extract demonstrated protective activity for albino rats' kidney and heart tissue against CCl_4-induced toxicity *in vivo* (Ganie et al., 2016). *C. monogyna* extract at 100–75 μg/mL concentrations exhibited better antiproliferative activity against C6 cell lines than 5-flurouracil drug (5-FU) and cisplatin, and also demonstrated considerable antiproliferative activity against HeLa cells (Yaglioglu et al., 2016). Ethanolic *C. meyeri* flower extracts, which contained flavonoids and procyanidins and had high *in vitro* antioxidant capacity in DPPH•, β-carotene–linoleic acid and TPC assays, also demonstrated antiproliferative activity against PC3 and PC14 cells and decreased the levels of serum alanine aminotransferase and aspartate aminotransferase in the blood of partially hepatectomized rats (Ozay et. al., 2015). Thus, the extracts were suggested as protective agents against partial hepatectomy-induced liver injury in rats and inhibitors of the proliferation of human non-small lung cancer cells.

Recently isolated from the fruit of *C. pinnatifida* phenylpropanoids crataegusoids (Table 2) were cytotoxic against human hepatocellular carcinoma cells HepG2 and Hep3B, while crataegusoids C and D with two methoxy groups at C-3′ most remarkably induced apoptosis in HepG2 cells indicating on structure-activity relationships (Guo et al., 2018). Finally, the hydroxy-olean-12-en-28-oic acid (HOA) triterpenoids from hawthorn berry, namely 3β,6β,18β,23-tetraHOA, 2β,3β,6β,18β-tetraHOA and 2 α,3 β,6 β,18 β,23-pentaHOA were potent inhibitors of HepG2 and MCF-7 cells, with the EC_{50} values lower than 5 μM (Qiao et al., 2015).

6. Neuroprotective effects

Neuroprotective effects of sesquineolignans (Table 2) isolated from the hydroethanolic (70%) extract of *C. pinnatifida* var. *major* seeds towards H_2O_2-induced damage in human neuroblastoma SH-SY5Y cells were recently reported by Huang et al. (2018a, b). All of these exhibited significant neuroprotective activity, compared with trolox, while 6 compounds demonstrated the survival rate of 90.74% at the 50 μM concentration, by inhibiting cellular apoptosis determined by Hoechst 33258 staining and annexin V/PI analysis (Huang et al., 2018a). Sesquineolignans also inhibited β-amyloid aggregation; (7′*S*, 8′*R*, 8*R*)-isolariciresinol-9′-*β*-*D*-glucopyranoside and lyoniside were stronger inhibitors of $A\beta_{1-42}$ aggregation than curcumin (Huang et al., 2018b). Possible mechanism of interactions was investigated by molecular docking.

The potential of hawthorn as natural antidepressant was also reported. The levels of typical markers of depression in animal models, monoamine oxidase B and reduced spine numbers along neuronal dendrites, were improved by chlorogenic acid or the extract of *C. pinnatifida* both *in vivo* using mice model with induced depression-like phenotypes by daily injection of stress hormone, and *in vitro* using cultured astrocyte type I clone C8-D1A cells (Lim et al., 2018). A protective effect of vitexin, which is one of the most important flavonoid in hawthorn leaves, against neurotoxicity has also been reported; however, the mechanisms of action remain elusive. Systemic vitexin treatment significantly reduced neurological deficit, cerebral infarct volume and neuronal damage when compared with the ischemia/reperfusion (I/R) injury mice. Vitexin markedly upregulated extracellular signal-regulated kinases (p-ERK1/2), downregulated c-Jun N-terminal kinases (p-INK) and p38 phosphorylation (p-p38), increased B-cell lymphoma 2 (Bcl-2) expression and suppressed the overexpression of Bax in the I/R mice, thus, protecting brain against cerebral I/R injury

regulated by mitogen-activated protein kinase (MAPK) and apoptosis signaling pathways (Wang et al., 2015a). Vitexin presented no cytotoxicity in RAW 264.7 cells and effectively reduced leukocyte migration *in vivo*, TNF-α, IL-1β, PGE2 and NO releases and increased in IL-10 release in the LPS-challenged mice; it was also able to regulate transcriptional factors for pro-inflammatory mediators, by reducing the expression of p-p38, p-ERK1/2 and p-JNK (Rosa et al., 2016). Chen et al. (2016) also attempted to obtain evidence on mechanisms using Sprague Dawley rats and human PC12 pheochromocytoma neurosecretory cells with isoflurane-induced neurotoxicity and cytotoxicity, respectively, and suggested that vitexin mediates by targeting the transient receptor potential cation channel subfamily V member 1 gene (TRPV1) and N-methyl D-aspartate receptor subtype 2B protein (NR2B) signaling pathways. The study of Hu et al. (2018) demonstrated that vitexin from *C. pinnatifida* protected dopaminergic neurons against methyl-4-phenylpyridine/1-methyl-4-phenyl-1,2,3,-6-tetrahydropyridine (MPP+/MPTP)-induced neurotoxicity through the activation of phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase B (PI3K/Akt) signaling pathway, and these findings may facilitate the clinical application of vitexin in the Parkinson's disease therapy.

The combination of Radix Puerariae and hawthorn fruit tested with diabetic rats showed the following effects: (1) reduced random blood glucose, TC, TG and improved glucose tolerance; (2) reversed the loss in body weights; (3) reduced depressive-like behavior as measured by open field, the elevated plus-maze, locomotor activity, and forced swimming tests; and (5) upregulated brain-derived neurotrophic factor and activated extracellular signal-regulated protein kinase (Luo et al., 2016). Vitexin exerted behaviorally-specific antinociceptive effect against postoperative pain using a mouse model with surgical incision on the right hindpaw, which was mediated through opioid and GABA(A) receptors (Zhu et al., 2019). It was observed that *C. pinnatifida* containing Naodesheng formula could reverse most of the cerebral ischemia reperfusion induced imbalanced metabolites in brain tissue, plasma and urine, which indicates on its protective effect on ischemic stroke rats by mechanisms involving multiple metabolic pathways, including energy metabolism, amino acid metabolism, oxidative stress and inflammatory injury (Luo et al., 2016). Most recently potential efficacy of Naodesheng for treating Alzheimer's disease was evaluated by combined machine learning, molecular docking, and pharmacophore mapping, and as a result constituent-target network, constituent-target-target network and target-biological pathway network was built for this formula as the virtual screening and network pharmacology method for the first time (Pang et al., 2018). *C. oxyacantha* extract ameliorated some seizure parameters in penicillin-induced epilepsy in gerbils; however, further and more advanced physiologic and neurochemical studies are required to determine the mechanisms involved (Cakir et al., 2016).

The compounds from *C. oxyacantha* effectively inhibited AChE, from IC_{50} = 5.22 μM (β-sitosterol-3-*O*-β-D-glucopyranoside) to 44.47 μM, and BChE activity with IC_{50} = 0.55–15.36 μM. In addition, docking procedures with Genetic Optimization for Ligand Docking suit v5.4.1 were applied to study the inhibition mechanism, while software admetSAR predicted that both of the isolated compounds can cross blood brain barrier (BBB+) (Ali et al., 2017). AChE catalyzes the breakdown of acetylcholine and of some other choline esters that function as neurotransmitters, while BChE in plasma can be used as a liver function test in both hypercholinesterasemia and hypocholinesterasemia. Potential antioxidant, hypoglycemic, and neuroprotective effects of acidified methanol or ethanol extracts of *C. microphylla* stem barks and leaves were supported by evaluating their AChE, tyrosinase and α-glucosidase inhibitory, DPPH$^{\bullet}$ scavenging capacity and protective activity against hydroxyl radicals-induced DNA strand scission (Renda et al., 2018). Macroporous resin Diaion HP-20 adsorption chromatography was applied to obtain rich in phenolics extract from hawthorn fruit peel (EPHF), which contained ideain, epicatechin and chlorogenic acid as the main constituents (179.4, 40.9, and 10.0 mg/g, respectively) and exhibited strong antioxidant (ORAC = 11.65 μM TE/mg, IC_{50} in DPPH$^{\bullet}$ scavenging = 6.72 μg/mL) and AChE inhibitory (IC_{50} = 11.72 μg/mL) activities (Wu et al., 2017). Methanolic extract of *C. microphylla* was shown as a good source of antioxidant, antimicrobial, antidiabetic, anticholinesterase, and anticancer agents in various *in vitro* assays (Aksoy-Sagirli at al., 2017).

7. Skin protective and other health effects

The extract from the Greek hawthorn *C. pycnoloba* was tested as a potent inhibitor of melanin synthesis during early zebrafish embryo development. The activity based subfractionation enabled to identify 3 melanogenesis inhibiting dibenzofurans (Table 2), acting not *via* inhibition of tyrosinase or interfering with neural crest differentiation or migration, but *via* binding to the aryl hydrocarbon receptor by activating its signaling pathway and causing the induction of the target genes expression (Agalou et al., 2018). Ursolic aldehyde, isolated from the active fragments of *C. pycnoloba*, had no melanin synthesis inhibition activity. The assays with HaCaT human keratinocytes, normal human dermal fibroblasts (HDFs), and mice showed that hawthorn polyphenol extract (HPE), containing chlorogenic acid, procyanidin B2, and epicatechin (13.5, 19.2, and 18.8% of the TPC, respectively), can prevent UVB radiation-induced skin photo-aging by promoting human cell proliferation *in vitro* and regulating matrix metallopeptidase expression and type I procollagen production *in vivo* (Liu et al., 2018). Ethanol extract from *C. pinnatifida* fruits (TPC = 61.31 mg/g, TFC = 25.42 mg/g) at 50 μg/mL reduced melanin contents by 8.5% while at 1,000 μg/mL reduced intracellular tyrosinase activity by 46.83%, thus suggesting that the extract could be used as a whitening agent in cosmetics (Park et al., 2017a). The mixture of *P. ginseng* and *C. pinnatifida* improved procollagen type I expression, diminished matrix metalloproteinase-1 secretion and improved various other human skin values associated with aging, wrinkle formation and moisture (Hwang et al., 2017). Creams with 5–15% of *C. pontica* leaf extract have a healing effect on dermal toxicity caused by T-2 toxin as it was shown by the study with Iranian rabbits (Kalantari et al., 2016). The penetration of active substances into the full undamaged human skin from the semisolid preparations containing *C. oxyacantha* extract was evaluated *ex vivo*. However, it was observed that, although the extract exhibited antimicrobial and antiradical activity, its compounds stay on the surface of the undamaged human skin, thus only traces of hyperoside and isoquercitrin were found in the epidermis (Stelmakienė et al., 2016).

The effects of *C. orientalis* M Bieber extract on serum oxidative status and alveolar bone loss in experimental periodontitis was studied *in vivo* and showed inhibitory effect on periodontal inflammation and alveolar bone loss by regulating total antioxidant (TAS)/oxidant (TOS) status and oxidative stress index levels in periodontal disease in rats when administered systemically (Hatipoglu et al., 2015). *C. azarolus* extract was active against herpes simplex virus-1 (HSV-1), and antiviral activity correlated with TPC ($R = 0.773$, $p < 0.001$) and free radical scavenging capacity ($R = -0.684$, $p < 0.01$) (Moradi et al., 2018). Hawthorn hyperoside (10, 50, 100 μmol/L) dose-dependently inhibited LPS-induced pro-

liferation and migration of human rheumatoid fibroblast-like synoviocytes (RA FLSs) *in vitro*. Furthermore, hyperoside decreased LPS-stimulated production of TNF-α, IL-6, IL-1 and MMP-9 in the cells, inhibited LPS-induced phosphorylation of p65 and IκBα, and suppressed nuclear translocation of p65 and DNA biding of NF-κB in the cells. Three-week administration of hyperoside significantly decreased the clinical scores, and alleviated synovial hyperplasia, inflammatory cell infiltration and cartilage damage on mouse with collagen-induced arthritis. Hyperoside inhibited LPS-induced proliferation, migration and inflammatory responses in RA FLSs *in vitro* by suppressing activation of the NF-κB signaling pathway, which contributes to the therapeutic effects observed in mice with collagen-induced arthritis (Jin et al., 2016).

In the study with male Sprague-Dawley rats hydroalcoholic extract of *C. azarolus* ssp. *aronia* fruit significantly lowered systolic blood pressure and phenylephrine maximal response and increased acetylcholine maximal response, serum SOD, and serum glutathione reductase in the renal artery-clipped group receiving vehicle. It was concluded that antihypertensive effects of extract may be partly due to antioxidant and NO releasing effects (Haydari et al., 2017). Ethyl acetate fraction of *C. dahurica* methanol extract demonstrated the greatest antioxidant activity while n-butanol fraction significantly accelerated the gastrointestinal transit in mice. Thus, this plant was suggested to serve as a good source of antioxidants and digestion-improving agents (Wang et al., 2018). Ethanolic extracts of *C. orientalis* leaves and berries inhibited cyclooxygenase-1 (COX-1) and 12-lipoxygenase (12-LOX), while its leaf extract showed a concentration dependent inhibition of COX-1 pathway products, 12-HHT and TXB2 (Šavikin et al., 2017).

Rhodiolae Kirliowii Radix et Rhizoma and *C. pinnatifida Fructus* may provide sources of potential antiviral compounds that was evidenced by hemagglutination inhibition activity on B human polyomaviruses BK KPyV and JCPyV VLPs and reducing their expression in infected cells (Chen et al., 2017). *C. oxycantha* buds fluid extract and the hydro-ethanolic macerate were active against thirty-due clinical strains of *U. urealyticum*, with MIC ranges of 15.6–250 and 15.6–62.5 μg/mL, respectively. Meanwhile, among the major purified flavonoids luteolin 3,7-diglucoside and apigenin-7-O-glucoside were the most active compounds with MICs 0.48–1.95 and 0.48–3.9 μg/mL, respectively (Bisignano et al., 2016). Ethanolic extract of *C. azarolus* var. *eu-azarolus* Maire leaves and its hexane, chloroform, and n-butanol fractions as well as ursolic acid, 3β-*O*-acetyl ursolic acid and quercetin 3-*O*-methyl ether showed variable antimicrobial activities against *E. coli*, *P. aeruginosa*, *S. aureus*, and *C. albicans* (Abu-Gharbieh and Shehab, 2017).

8. Toxicity of hawthorn preparations

Safety of *Crataegus* preparations has been proven by many studies and safe history of use. Some recent studies with *C. oxyacantha* extend the knowledge on this issue. Evaluation of *C. oxyacantha* fruit extract showed that it did not produce marked genotoxic effects at concentrations of 2.5 or 5 μg/mL in leukocytes and human liver hepatocellular carcinoma HepG2 cultured cells; however, at concentrations of 10 μg/mL or higher significant DNA damage and clastogenic/aneugenic responses were observed. The extract induced mutagenic effects in TA98 strain of *S. typhimurium* (Ames test) with metabolic activation at all tested concentrations (2.5 to 500 μg/mL). Consequently, under certain experimental conditions, the extract exerts genotoxic and clastogenic/aneugenic effects in human cells, and mutagenicity in bacterial cells (De Quadros et al., 2017). Previous *in vitro* findings were also confirmed by the study of Yonekubo et al. (2018) with *C. oxyacantha* extract, showing that in comet assay it did not markedly induce DNA damage in leukocytes and bone marrow cells; however, in the micronucleus test the extract produced a significant rise in micronucleated polychromatic erythrocytes (PCE) in a non-dose dependent manner. The PCE/normochromatic erythrocytes (NCE) ratio indicated no significant cytotoxicity under applied experimental conditions, however, *C. oxyacantha* fruits extract exhibited weak clastogenic and/or aneugenic effects in bone marrow cells of male mice (Yonekubo et al., 2018). It suggests that prolonged or high dose use of such extracts needs to be undertaken with caution. Most recently, the electrocardiographic effects of hawthorn in healthy adult volunteers was tested and it was concluded that a single dose of oral *C. oxyacantha* had no effect on electrocardiographic parameters in healthy volunteers (Trexler et al., 2018).

9. Processing, quality control and other uses

Raw plant material and natural products should be carefully prepared, considering various aspects, e.g. protection of sensitive active ingredients, convenient forms for dosing and administration, standardization in terms of concentration of active ingredients and others. Some recent studies have focused on such issues.

Drying is an important process for many natural ingredients for medicines and food supplements. Aral and Bese (2016) investigated convection-drying of *Crataegus* spp. fruit at 50, 60 70 °C with air velocities of 0.5, 0.9 and 1.3 m/s and applied different mathematical models for the experimental data. They observed that while the shrinkage decreased, the rehydration ratio increased with increasing air temperature and air velocity. Microwave-drying, oven-drying at 50 and 70 °C, sun-drying and shade-drying were compared for the fresh fruits of *C. azarolus* and *C. orientalis*. The results showed that antioxidant capacity increased, and at the same time the TPC decreased with the temperature increase in oven drying, whereas in other drying methods (microwave, sun and shade-drying) the TPC increased; meanwhile, vitamin C content decreased in all samples. The samples dried in a microwave appeared to have the highest antioxidant capacity and it was concluded that it was the best method for preserving bioactive phytochemicals (Saadatian et al., 2016). Freeze-drying was reported to be better than hot air drying for hawthorn (*C. pinnatifida*) in terms of antioxidant, α-glucosidase inhibitory potential, the TPC/TFC values and color (Kwon, 2016).

Immersing of hawthorn fruits in a glycine betaine solution for 15 min at 20 °C effectively prevented fruit chilling injury and improved nutritional characteristics at low-temperature storage (Razayi et al., 2018). It significantly delayed fruit pitting development during storage at 1 °C for 20 days, increased accumulation of glycine betaine, proline, phenols, flavonoids, anthocyanins, and ascorbic acid, which was concurrent with higher SOD, catalase (CAT), ascorbate peroxidase (APX), and $DPPH^{\bullet}$ scavenging capacity.

Emulsions prepared from the extracted from hawthorn pectin and candelilla wax were used as an edible film for treating *Pleurotus ostreatus* mushroom. This process reduced weight loss, improved firmness, and lightness, compared to untreated mushroom slices during 20 days of storage at 4 °C (Lozano-Grande et al., 2016). The functional Ag-Fe_3O_4 nanocomposites, which were prepared *via* one-pot hydrothermal method using aqueous extract of *C. pinnatifida* leaves as reducing and capping agent, exhibited

sustainable antibacterial activity against *S. aureus* and *E. coli*. The nanocomposites can be easily separated from the medium by a magnet and continues to exhibit recyclable antibacterial activity (Li and Yang, 2016). Tonic wine was produced by maceration of hawthorn fruits in red wine; as a result its TPC and antioxidant capacity remarkably increased (Muresan et al., 2016). Effects of 2,4-dichlorophenoxyacetic acid (2,4-D) combined to 6-benzylaminopurine (BAP) on callus induction, TPC and ascorbic acid production, as well as antioxidant activities in *C. azarolus* L. var. *aronia* leaf tissue cultures were assessed and it was found that the use of high level of 2,4-D over BAP could enhance the quality even more than the quantity of bioactive compounds in hawthorn leaf callus (Chaabani et al., 2015). The microcapsules containing 751 mg/g of *C. monogyna* bark procyanidins, mainly (-)-epicatechin, dimer B2, and trimer C1, were produced by spray drying using inulin and maltodextrin as encapsulants (Wyspiańska et al., 2017). The addition of *C. monogyna* phenolic-rich extracts significantly improved the oxidative stability of cooked pork patties as measured by TBARS and hexanal production, and the degree of consumer satisfaction regarding product's odor perception (Akcan et al, 2017). Ethanolic extract of *C. monogyna* berry was more effective than synthetic antioxidant BHA in reducing lipid oxidation and protein degradation, as well as for maintaining firmness and consistency of minced pork during 6 days of refrigeration at 4 °C (Papuc et al., 2018).

For quality control purposes, HPLC analysis was established for chlorogenic acid and hyperoside, which are among the major compounds in Crataegi fructus; the average contents (w/w %) of these compounds in the 31 batches of products from Korea and China were 0.0438 and 0.0416%, and 0.0399 and 0.0325%, respectively (Wen et al., 2016). An accurate and advanced method has been established for the simultaneous determination of chlorogenic acid, vitexin and its 4″-*O*-glucoside, 2″-*O*-rhamnoside, orientoside, rutin and hyperoside in *C. pinnatifida* leaves. Under optimized conditions the yields of these phytochemicals were 0.46, 0.30, 0.38, 4.37, 0.033, 0.036, and 1.19 mg/g, respectively, while DPPH$^{\bullet}$ and ABTS$^{\bullet+}$ scavenging and reducing power of extract were 0.69 mg/mL (IC_{50}), 0.86 mM TE, and 0.24 mg/mL (IC_{50}), respectively (Luo et al., 2015). A simple, sensitive liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, which may serve for evaluating the pharmacokinetics, was developed and fully validated for the simultaneous determination of rutin, vitexin and its glycosides, hyperoside, shanyenoside in rat plasma after intravenous administration of hawthorn leaves flavonoids using lysionotin as an internal standard (Zhu et al., 2015).]

10. Conclusion

This review clearly shows that hawthorns remain an interesting and important topic both from the scientific investigation and practical application points of view. Recent studies of *Crataegus* spp. were focused on various aspects, including phytochemical characterization of different plant anatomical parts and drug forms, variations of bioactive compounds and antioxidant activities between plant species and cultivars from different origins, health benefits and some analytical, quality control and processing issues. Identification of new bioactive phytochemicals, particularly those belonging to non-phenolic structures, as well as intensive attempts for explaining the mechanisms in the treatment of various diseases and disorders with hawthorn preparations, extracts, separated fractions and purified compounds may be recognized as important required studies that would significantly complement the existing knowledge on *Crataegus* spp. in particular and natural products in general. In addition, the findings of recent years provide new ideas and suggest the trends for further studies of *Crataegus* spp.

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