Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Review

Biological activities and health-promoting effects of *Pyracantha* genus: a key approach to the phytochemical's potential

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Received April 9, 2020; **Accepted** May 2, 2020; **Published** June 25, 2020

Doi: http://dx.doi.org/10.14715/cmb/2020.66.4.4

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Abstract: *Pyracantha* spp. are commonly called firethorn, and attract human attention due to their colorful berries. These berries are eaten globally as a traditional remedy for treating different stomach abnormalities, and as a cooking ingredient for folk diets. The present review aims to provide an overview on *Pyracantha* genus' geographical distribution and botanical description, traditional uses, phytochemical composition, biological activities and safety issues. Several biological activities have been reported to *Pyracantha* species, namely antioxidant, anti-inflammatory, antimicrobial, larvicidal and cytotoxic properties, most of them attributed to the use of their fruits. *Pyracantha* species phytochemical composition reveal the presence of interesting bioactive molecules, such as pyracrenic acid and fortuneanosides. The currently reported biological activities to these plants derive from *in vitro* and *in vivo* studies, so that clinical trials are needed to confirm these preclinical results. Nonetheless, *Pyracantha* species can be suggested as a safe herb useful to develop future drug formulations and functional foods.

Key words: *Pyracantha* genus; Pyracrenic acid; Fortuneanoside; Phytochemicals; Biological effects.

Introduction

Pyracantha genus is an evergreen, thorny shrub belonging to the Rosaceae family, widely used in gardening and landscaping (1). The genus is commonly called as 'firethorn' due to the presence of dense poisonous thorns when pierce the human skin causes severe pain and inflammation. Originally introduced and planted as garden ornamentals, *Pyracantha* genus appears to house about 10 species (2-5). However, the exact number of species is unclear as there are many synonyms inconsistently used in the literature. Because of aesthetic values and presence of thorns, these plants are popularly used for making fences and walls.

In this sense, the present review aims to provide an overview on *Pyracantha* spp geographical distribution, botanical description, traditional uses, phytochemical composition, biological activities and safety issues.

Geographical distribution

Pyracantha spp. prefer warm temperate (Mediterranean) to cool, subtropical climates, with many species preferring cool subtropical climates (6-8). *Pyracantha* spp. are native to an area extending from Southwest Europe east to Southeast Asia. Various *Pyracantha* species are broadly distributed from the Eastern Mediterranean region and central Europe across Asia to China and Taiwan (9) (Table 1).

Botanical description

Plants under *Pyracantha* genus are thick shrub to small tree (1-4 m tall), occasionally reaching up to 6 m

Table 1. Species, common names and Distribution of *Pyracantha* species.

Pyracantha species	Common name	Distribution	Ref.
P. angustifolia (Franch.) C. K. Schneid.	Narrow leaf firethorn, Slender firethorn and Woolly firethorn	Chinese provinces of Guizhou, Hubei, Sichuan, Xizang, Yunnan and Zhejiang; central Argentina	(62, 63)
P. atalantioides (Hance) Stapf	Gigg's firethorn and Sichuan firethorn	Southeastern and western China	(62)
P. coccinea M. Roem.	Scarlet firethorn	Temperate Asia and Europe (Iran, Lebanon, Turkey, Armenia, Azerbaijan, Georgia, Ukraine, Albania, Bulgaria, Former Yugoslavia, Greece, France, Spain, central and southern Italy)	(30)
P. crenatoserrata (Hance) Rehder	Huo ji (China)	Chinese provinces of Fujian, Guangxi, Guizhou, Henan, Hubei, Hunan, Jiangsu, Shaanxi, Sichuan, Xizang, Yunnan and Zhejiang	(10)
P. crenulata (Roxb. ex D. Don) M. Roem.	Himalayan firethorn, Chhota seb,Nepalese firethorn, Indian hawthorn, "Ghingharu"	Temperate Himalayas; Chinese provinces; Bhutan and India	(20, 64-66)
P. densiflora T. T. Yu		China	(10)
P. fortuneana (Maxim.) H. L. Li	Broadleaf firethorn	Central China	(10)
P. inermis J. E. Vidal		China	(10)
P. koidzumii (Hayata) Rehder	Red berry firethorn, Formosa firethorn	Taiwan	(10, 26)
P. rogersiana (A. B. Jacks.) Coltm.-Rog.	Asian firethorn	Western China	(10)

in height and spreading up to 5 m across. Stem is erect to divergent or bent at a sharp angle, grayish bark in color. Plants are usually with long and short branches, glabrous or tormentous. Thorns are present mostly on short branches. Leaves are sessile or shortly petiolate, stipulate, simple, alternate, lanceolate to ovate up to 5 cm long, dark green, pubescent, margin crenulate, serrulate, or entire; venation camptodromous. Inflorescence terminal, compound corymb, many flowered; peduncle sub-glabrous to pubescent. Flowers are white to creamy white, blooms in spring and summer, pentamerous, pedicellate, bracteate, bract caduceus, lanceolate; bracteoles present; sepals 5, triangular, persistent, abaxially pubescent when young, apex acute; petals 5, ovate to sub-orbicular to broadly elliptic, white to creamy white; stamens 15-20, epigynous, filament 2-4 mm, shorter than petals, anthers yellow, dorsifixed, bilocular; hypanthium campanulate; carpels 5, syncarpous, ovary pubescent, 5 locular, ovules 2 in each locule; placentation axile; style free, nearly equal to stamen. Fruit fleshy pome, looks like tiny apple, 5-9 mm in diameter, red-to-orange color, sometimes yellow, glabrous. Seeds are brown and irregular in shape (4, 10).

Traditional uses

Plants of *Pyracantha* genus are used in traditional cultures in countries where they were originally endemic. They have been used in China for more than 1700 years as a food source, and have also been used as food in the Western Himalayas. At present, fruit juice, fruit wine and preserved fruit from these plants remain popular (11, 12).

Pyracantha fortuneana (Maxim.) H. L. Li is used as skin-whitening agent in cosmetics in Japan (13), and *Pyracantha crenulata* (Roxb. ex D. Don) M. Roem. is a fuel in Himalayan countries (11). Nowadays, plants of *Pyracantha* genus are popular in countries with a Mediterranean climate as a landscape ornamental (14).

In Ayurvedic medicine, *Pyracantha* spp. is used in the treatment of a number of disorders, including hepatic, stomach and skin diseases (15).

In traditional herbal medicine in some cultures, 4 species of *Pyracantha* genus are used. In the traditional medicine of the Indian Himalayas, *P. crenulata* fruits are often prescribed for the treatment of hypertension, arteriosclerosis, angina, diabetes, pregnant anemia, stomach disorders, including constipation, and externally in the form of juice for the treatment of earache (16-19). In traditional medicine of Nepal (20) and Indian rural community (21), the fruits of this plant are eaten in cases of dysentery. In Uttarakhand, bark of this plant is recommended for heavy bleeding during menstrual cycles (22). Also leaf paste of *P. crenulata* is used for burns (23). In Central Himalaya, *P. crenulata* roots are used in bathing for body pain (24). In traditional Chinese Medicine, *P. fortuneana* plants are used as a popular remedy. Fruits of this plant are recommended for oral administration for the treatment of dyspepsia and dysentery or for externally for sores relief (13, 25). *Pyracantha koidzumii* (Hayata) Rehder is used in dysmenorrhea (26). In Europe, *P. coccinea* fruits are taken for medicinal use as heart soother (27). Leaves of this plant are used in diarrhea and urinary diseases in Turkey (27, 28). *P. coccinea* are also used in veterinary medicine for diarrhea (27).

Phytochemical composition

Several studies showed the presence of phytochemicals, like glycosides, carbohydrates, steroids, flavonoids, phenolics, resins and tannins in *Pyracantha* spp. (18, 29-31). For example, Fico, A (32) found phenolic acids, such as hyperoside, isoquercitrin, quercetin and rutin in *P. coccinea* fruits. They also found that the flavonoids profile of *P. coccinea* showed marked differences between aerial and hypogeal parts of the plant. *P. fortuneana* fruits were also known to contain several types of polyphenols, such as cyanidins (33), biphenyl glycosides (34, 35), fortuneanosides A to F (34-36), acylphloroglucinol glycosides (34), and dibenzofuran glycosides derivatives (34, 35). The ripe fruit of *Pyracantha angustifolia* (Franch.) C. K. Schneid. constituted the best practical source for the isolation of pro-γ-carotene and has been a good source for prolycopene (37). A new compound, pyracrenic acid, isolated from *P. crenulata* bark revealed to be a potent anti-inflammatory agent (38). Quiroga, Bou (39) reported that linoleic (61.1%), oleic (17.3%) and palmitic (17.4 %) acids were the major fatty acids present in *P. crenulata* seed extract. Two compounds, *viz.* 3,6-dihydroxy-2,4-dimethoxy-dibenzofuran and 3,4-dihydroxy-5-methoxybiphenyl-2'-*O*-D-glucopyranoside were isolated from *P. koidzumii* (26). Overall, in the genus *Pyracantha*'s fruiting and flowering parts, around 30 metabolites could be found. Pyracanthoside and rutin, two flavonoids, appear during all stages of the plant life cycle (32). Representative phytochemicals present in *Pyracantha* spp. are shown in Figure 1.

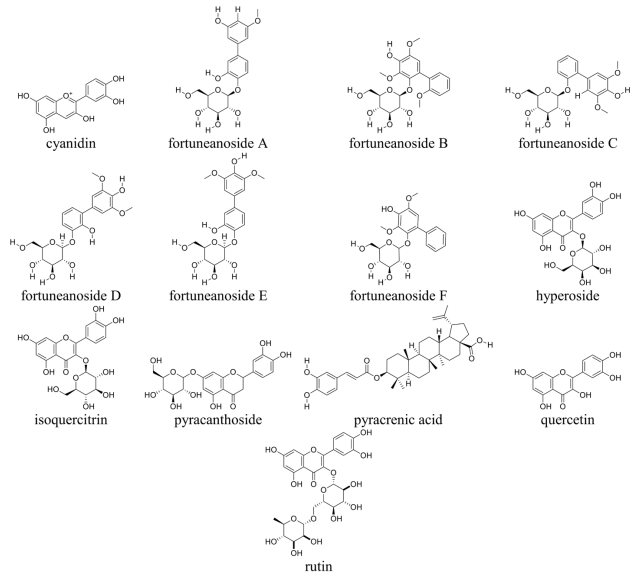

Figure 1. Representative phytochemicals present in *Pyracantha* species.

Biological activities

Several bioactive effects have been reported to *Pyracantha* spp., with the most prominent ones being their antioxidant, antimicrobial, larvicidal, cytotoxic, and anti-inflammatory effects. In the following sections are described the biological activities of the most common *Pyracantha* spp., summarized in Figure 2.

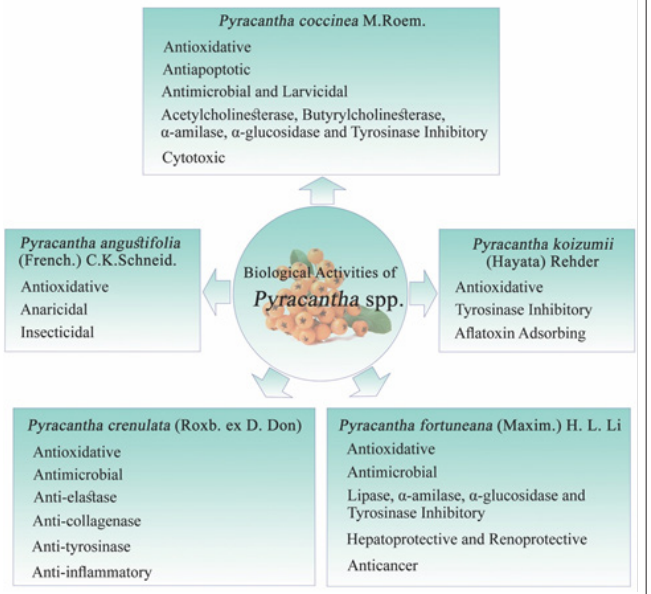

Figure 2. Biological activities of different *Pyracantha* spp.

Pyracantha angustifolia (Franch.) C.K.Schneid.

Kim, Park (40) reported that *P. angustifolia* leaves methanol extract (at 10, 000 ppm) exhibited insecticidal and acaricidal activities against *Tetranychus urticae*, *Aphis gossypii*, *Myzus persicae*, *Trialeurodes vaporariorum*, and *Panonychus citri*. The antioxidant activity, total polyphenols and electron donating abilities of methanol extract, methylene chloride, ethyl acetate, and methanol fractions of *P. angustifolia* were reported by Lee (29). The extract exhibited superoxide radical as well as hydrogen peroxide (H_2O_2) scavenging activity. The highest total polyphenol contents (2007.30±109.28 µg GAE/mL) were found in 70% methanol extract. Moreover, 70% methanol extract also showed highest electron donating abilities (79.07±7.31) and superoxide radical removal ability (0.018±0.003). Furthermore, the methylene chloride fraction exhibited maximum H_2O_2 decomposition (0.0027±0.0015) among the extracts/fractions.

Pyracantha coccinea M. Roem.

Antioxidant activity of *P. coccinea* was reported by several authors (9, 30, 41). Min, Yeon (41) reported that *P. coccinea* root extract (5 µg/ml), among all extracts tested [leaf, stalk and root for 6 days (1, 5 and 10 µg/ml respectively)] significantly increased blastocyst formation, total cell numbers and reduced apoptotic index in porcine parthenogenetic embryos. It decreased intracellular levels of reactive oxygen species (ROS) under H_2O_2-induced oxidative stress. Therefore, the improvement in the *in vitro* development of porcine parthenogenetic embryos was attributed to the *Pyracantha* root extract via its antioxidant and antiapoptotic properties. In other study, Keser (9) used different solvents to extract phytochemicals from *P. coccinea* fruit and determined antiradical activities by 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and hydroxyl radical scavenging assays. Ethanol, methanol and acetone extracts exhibited higher scavenging activity on ABTS when compared to

BHT, used as positive control, whereas methanol and ethanol extracts showed higher scavenging activity on DPPH compared to BHT. The extracts also showed better antioxidant activities than α- and δ-tocopherol, vitamins K and D, β-sitosterol, ergosterol, and stigmasterol. Sarikurkcu and Tepe (30) reported that the ethanol and water extracts of *P. coccinea* inhibited acetylcholinesterase, butyrylcholinesterase, α-amylase, α-glucosidase and tyrosinase effects. It was also observed that the scavenging potential on DPPH radical, ABTS radical cation, superoxide anion and nitric oxide was higher for the ethanol extract than that of water extract. Ethanol extracts also displayed higher activities in antioxidant power (FRAP), cupric ion reducing, ferric reducing, iron (III) to iron (II) reduction, and phosphomolybdenum assays. The work suggested its possible therapeutic use against Alzheimer's disease.

To *P. coccinea* extracts, interesting antimicrobial (27, 42) and larvicidal (43) effects have been also reported. Turker, Yildirim (27) reported that *P. coccinea* extracts (from 8 solvents) exhibited antibacterial activity against *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Streptococcus pyogenes*. Among the extracts, fruits extracted in hot ethanol exhibited prominent antibacterial activities against the 3 tested bacteria. Kokubun, Harborne (42) reported that *P. coccinea* sapwood-derived dibenzofuran phytoalexin, 9-hydroxyeriobofuran exhibited antifungal activity against *Alternaria alternata, Botrytis cinerea* and *Fusarium culmorum*, comparable to that of cotonefurans. 9-hydroxyeriobofuran (10, 20, 50 and 100 µg/ml) inhibited fungal spore germination with, respectively, 100% 100% and 98% inhibition (ED_{50} values of 44, 39 and 49 µg/ml), at 10 µg/ml, against the 3 fungi. Koc, Evren (43) reported that *P. coccinea* fruit methanol extract (62.5–1000 ppm) exerted larvicidal activity against second instar larvae of *Culex pipiens*. At 62.5 ppm, following 96 h of exposure, the extract showed larvicidal activity (0.46±0.26%) with LC_{50} and LC_{90} values of 32110.12 and 808652.32 ppm, respectively.

P. coccinea fruits methanolic extract also revealed cytotoxic effectsVahabi, Monajemi (44). In that study, it was reported a weak cytotoxic effect (with highest activity at 800 µg/ml) on Hela cell lines (MTT assay). The antioxidant activity (DPPH assay), and total phenolic contents (Folin-Ciocalteu assay) displayed by the methanol extract were found to be higher when compared to the aqueous extract.

Pyracantha crenulata (Roxb. ex D. Don) M. Roem.

Several studies have reported the antioxidant activity of *P. crenulata* (45-47). Pal, Arun Kumar (46) used methanol extract (0.5, 1.0, 1.5 and 2.0 mg/ml) of *P. crenulata* mature fruits and reported radical scavenging activities. In addition, *P. crenulata* possessed higher levels of lycopene and β-carotene when compared to the another studied plant *Berberis asiatica*. Saklani, Badhani (47) reported the antioxidant activity of *P. crenulata* fruits through DPPH [19.18±0.14 ascorbic acid equivalent (AAE)/100 g fw], ABTS (4.41±0.03 AAE/100 g fw) and ferric ion reducing antioxidant power (FRAP) (2.34±0.01 AAE/100 g fw) assays. Besides, it exhibited total phenols, total flavonoids, total anthocyanins, vitamin C and gallic acid at the levels of 5.59±0.05 mg GAE/g fw, 5.46±0.04 mg/g fw, 0.44±0.05 mg/100 g fw, 3.30±0.34 mg/100 g fw and 10.15±1.40 mg/100 g fw, respectively. Singh, Lily (45) reported that *P. crenulata* fruit 80% aqueous acetone extract exhibit free radical scavenging activities (through DPPH, ABTS, linoleate hydroperoxyl and superoxide radicals), FRAP, ferrous metal chelating capacity, anti-elastase, anti-collagenase, anti-tyrosinase and anti-inflammatory activities. The total phenolics and total flavonoids content found were, respectively, 144.16±3.50 mg GAE/100 g fw and 303.75±3.50 mg CE/100 g fw. Otsuka, Fujioka (38) isolated pyracrenic acid from *P. crenulata* bark and found that it displayed anti-inflammatory activity (in the fertile egg method) at doses of 10, 200 and 400 µg/disc, with inhibition percentage of 13.8%, 38% and 43.1%, respectively, and survival ratios of embryos with 19/20, 16/20, 18/20, respectively. In addition, it also inhibited granulation tissue formation by the fertile egg method, at 50 mg/kg, when orally administered in rats.

Saklani and Chandra (18) reported that *P. crenulata* fruit pulp ethanolic extract exhibit antimicrobial activities against *Shigella flexneri*, *Escherichia coli* and *S. pyogenes*. The crude protein, crude fiber and carbohydrates contents in the extract were found to be 5.13%, 7.40% and 24.88%, respectively. The extract was also reported to contain phenolics, saponins and flavonoids at 1.83%, 1.56% and 3.12%, respectively.

Pyracantha fortuneana (Maxim.) H. L. Li

Diverse biological activities have been reported to *P. fortuneana*. Zhao, Lei (48) reported the antioxidant activity of *P. fortuneana* fruit water-soluble polymeric polyphenolic fractions on HepG(2) cells. The authors also reported an increase in cell antioxidant activities using peroxyl radical-induced DCFH oxidation method with higher decrement being stated at EC_{50} values of 2.91. The *in vivo* antioxidant benefit of small molecular polyphenols was attributed to the additive effects conferred by the proanthocyanidins present in fractions. In another study, the same group also assessed the total polyphenolic content (TPC), total antioxidant activity (TAA) and chromatographic profiling of the plant extract through response surface methodology (RSM) and solvent optimization, in order to enhance the *P. fortuneana* fruits applicability as nutraceutical in food industries (49).

Wang, Ye (31) with the help of high-pressure liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (HPLC-QTOF-MS/MS) profiling identified 7 flavonoids, 6 phenolic acids, 7 organic acids, 3 tannins, 1 terpene, and 1 alkaloid from *P. fortuneana* fruit (50% acetone extract) and reported antioxidant and α-glucosidase inhibitory activities. Wei, Chai (50) extracted proanthocyanidins from *P. fortuneana* fruit and reported α-glucosidase inhibition (IC_{50} 0.15 µg/mL) in a non-competitive manner. Dai, Zhou (35) reported the isolation of biphenyl glycosides, fortuneanosides A to E from *P. fortuneana* fruit and observed that fortuneanoside D inhibited tyrosinase (IC_{50}=0.07 mM) most efficiently when compared to arbutin (IC_{50}=0.23 mM). Xu, Zhao (51) reported that *P. fortuneana* fruit extract reduced lactulose/mannitol ratio and glucose transporter 2

(GLUT2), improved tight junction proteins, modulated bacterial groups linked with gut barrier integrity, such as *Actinobacteria*, *Bacteroidaceae*, *Corynebacteriaceae*, *Lactobacillaceae*, and S24-7, and inhibited α-amylase, α-glucosidase, and lipase enzymes. Moreover, the same group reported, in rodents, a decrease in body weight, triacylglycerol, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and malondialdehyde (MDA) levels, and elevation in high-density lipoprotein cholesterol (HDL-c), glutathione peroxidase (GPx), and superoxide dismutase (SOD) (52). These results markedly suggested the *P. fortuneana* fruit potential against hyperlipidemia, obesity and oxidative stress.

Peng, Guo (25) reported that selenium-enriched *P. fortuneana* polysaccharides (Se-PFPs) exhibit antioxidant and hepatoprotective effects. In mouse liver, at 3 concentrations (1.35, 2.7 and 5.4 g/kg body weight) it was stated a significant inhibition on cyclophosphamide-induced micronucleus formation in both bone marrow and peripheral blood, cytochrome P450 1A and increased SOD and GPx activities. In the same way, Yuan, Li (53) reported that Se-PFPs decreased alanine aminotransferase (ALT), aspartate aminotransferase (AST), LDH, TC, triglycerides in serum, while elevated the SOD, GPx, glutathione and catalase activities. The same group also reported that Se-PFPs inhibited the triple-negative breast cancer, MDA-MB-231 cells growth in a dose-dependent manner at G2 phase, increased p53, B-cell lymphoma-2 (Bcl-2)-associated X Protein (Bax), Puma and Noxa, Bax/Bcl2 ratio, caspases 3/9, and decreased Bcl2. More interestingly, Se-PFPs was reported as containing carbohydrates [93.7% (w/w)], uronic acid [2.1% (w/w)] and selenium [3.7 μg/g]. (54). Similarly, Sun, Dong (55) reported that Se-PFPs reduced cyclin D1, Bcl-2 and matrix metallopeptidase 9 (MMP-9), N-cadherin, vimentin, ZEB1 and ZEB2 and increased the cleavage of PARP, caspase-3, and -9, E-cadherin and cytokeratin 19 in HEY and SKOV3 human ovarian cancer cells. The authors have proposed Se-PFPs as promising against ovarian cancer.

Ke, Yu (56) reported that *P. fortuneana* fruit extract (administered orally at 250 mg/kg) protected against the acute renal toxicity induced by cadmium chloride ($CdCl_2$) (6.5 mg/kg for 5 days) in rats. Critical parameters, like kidney weight, body weight, malondialdehyde (MDA), nitric oxide production, uric acid, urea, and creatinine, glutathione, SOD, catalase, GPx, Bcl-2 expression, Bax, TNF-α, Keap-1, Nrf2, HO-1, γ-GCS, GPx and NQO1 expression were also assessed. Sun, Wang (13) optimized the polyphenols extraction (by ultrasonic assisted extraction method) from *P. fortuneana* fruits and reported their antibacterial activity against *S. aureus* and *E. coli* (MIC values of 10 and 20 mg/mL, respectively). Mei, Wan (57) reported that *P. fortuneana* extract and the chloroform phase (among the 3 polar extract fractions), when administered orally, shortened the coagulation time of glass slide in mice. In addition, they also shortened the prothrombin time and recalcification time *in vitro*Mei, Wan (57).

Pyracantha koidzumii (Hayata) Rehder

Jiang, Chang (58) reported that *P. koidzumii* extracts exhibited less cytotoxicity than other natural products used in cosmetics, displayed promising cellular tyrosinase inhibitory activity (IC_{50}=54.8 μg/mL) and potent free radical scavenging activity against hydroxyl, superoxide, and ABTS anion radicals. *P. koidzumii* leaves and fruits contained, respectively, 3.55 and 0.23 g GAE/g extract of total phenolic contents. Lin, Chen (26) isolated 3,6-dihydroxy-2,4-dimethoxy-dibenzofuran and 3,4-dihydroxy-5-methoxybiphenyl-2'-*O*-D-glucopyranoside from *P. koidzumii* and observed that these compounds inhibited cellular tyrosinase in a dose-dependent manner. The compound 3,4-dihydroxy-5-methoxybiphenyl-2'-*O*-D-glucopyranoside exerted uncompetitive mixed-type inhibitor effects (against L-3,4-dihydroxyphenylalanine) with a K_m value of 0.262 mM. Ramales-Valderrama, Vázquez-Durán (59) reported that *P. koidzumii* biomasses (leaves, berries and leaves/berries mixture) adsorbed B-aflatoxins (AFB1 and AFB2) through electrostatic interaction. The highest aflatoxin uptakes were reported to be 86% and 82% at 6 h, respectively, for leaves and leaves/berries mixture biomasses. Hence, *P. koidzumii* biomasses-mediated biosorption could be viewed as an effective alternative strategy to remove B-aflatoxins.

Safety and adverse effects

Pyracantha spp. attracts human attention due to its colorful berries and those are eaten globally as traditional medicine and as a cooking ingredient. However, there is no in-depth report on their safety concerns and adverse effects. *P. crenulata* fruits are eaten by Indian rural community in several regions, with its powder being also mixed with yoghurt to treat bloody dysentery, thus clarifying its non-toxic properties (21). *P. angustifolia* leaf extract showed lesser effects while checking its insecticidal activities against *A. gossypii, M. persicae, T. vaporariorum, and P. citri*, revealing a higher survival rate after 72 h exposure at 10,000 ppm when compared to the control and other plants tested (40). In another study, *P. coccinea* fruit methanol extract was applied in mosquito larvae (*C. pipiens*) to determine its larvicidal/insecticidal effects, but no significant mortality was found even at the highest concentration (i.e. 1000 ppm) (43). Pretreatment with *P. fortuneana* fruit extract on kidney injury in $CdCl_2$-injected rats showed that it could significantly reduce $CdCl_2$-induced toxicities through increasing Nrf2, HO-1, γ-GCS, GSH-Px and NQO-1 expression (56). Thus, it was reported to be beneficial for treating renal toxicity caused by $CdCl_2$. This extract was also reported to have ameliorative effects on intestinal barrier dysfunction in high fat diet-induced Sprague Dawley rats without showing toxicity (52). Besides, *P. fortuneana* polysaccharides were found to enhance immune function and oxidative stress in mice (60). Of them, selenium containing polysaccharides could significantly reduce the tumor growth besides to confer preventive effects against CCl_4-induce liver injury in mice model without altering body weight (53, 54). Peng, Guo (25) reported that selenium containing polysaccharides administered to mice at doses up to 5.4g/kg body weight caused no detectable toxicity and death during the 30-day experiments. Medicinal plant polysaccharides are in general thought to be nontoxic, thus making them suitable for therapeutic applications

(61), and based on the several previous findings, it is undoubtedly clear that selenium containing polysaccharides from *Pyracantha* spp. can be used and considered as a safe naturally-derived therapeutic agent.

All previous studies with *Pyracantha* spp. evidenced its safety and non-toxicity as a traditional medicinal source. However, there are some rumors among rural/scientific communities on the possible plant toxicities. Thus, *Pyracantha* spp. can be suggested as a safe herbal source for developing future drug formulations and functional foods for human health promotion.

Conclusions and future perspectives

Pyracantha spp. are used in folk medicine for treating different human medical conditions, such as stomach abnormalities, hepatic and skin diseases. In addition, several biological properties have been attributed to the *Pyracantha* genus members, *viz.* antioxidant, anti-inflammatory, antimicrobial, larvicidal and cytotoxic effects. Many reports are available on specific *Pyracantha* spp. for their pharmacological benefits using various *in vitro* and *in vivo* animal models, most of them concentrated on the effects of its fruits. The use of these plants in folk medicine and its reported biological activities (*in vitro* and *in vivo*) are closely related to the plants' phytochemical composition. However, a scarce amount of studies is available elucidating some interesting phytochemicals found in *Pyracantha* spp. (i.e. pyracrenic acid and fortuneanosides). In addition, some *Pyracantha* spp. extracts and phytochemicals have revealed enzymatic inhibition abilities, and thus may be useful in pathologies such as hyperlipidemia, obesity and oxidative stress-related diseases. Thus, given the current insights, further studies are needed to determine the phytochemical composition of all plant parts of different *Pyracantha* spp. and to determine the biological activities of plants extracts and purified phytochemicals. Clinical trials should also be conducted to confirm the preclinical studies findings. Anyway, *Pyracantha* spp. can be viewed as safe plants, useful to develop future drug formulations and functional foods.

Funding
This research received no external funding.

Acknowledgements
This work was supported by CONICYT PIA/APOYO CCTE AFB170007.

Conflicts of Interest
The authors declare no conflict of interest.

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