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Bioactive components and biological properties of cornelian cherry (*Cornus mas* L.): A comprehensive review

Hatice Merve Bayram, S. Arda Ozturkcan*

Istanbul Gelisim University, School of Health Sciences, Department of Nutrition and Dietetics, Istanbul, Turkey

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ABSTRACT

Today, medicinal plants are very popular due to preventing many diseases and associated complications. *Cornus mas* L. (CM), is a member of Cornaceae family, is widely used in folk medicine for the treatment of a wide range of diseases such as diabetes, digestive ailments, anemia, liver and renal diseases, among others. The aim of this review is to present an overview of CM's biological properties and usefulness as a nutritional supplement. CM fruits contain high levels of anthocyanins and iridoids while the leaves contain higher phenolic acids. The therapeutic effects of CM include anti (-oxidant, -microbial, -diabetic, -atherosclerosis, -obesity, -glaucoma); (cyto-, neuro-, cardio-, liver-, renal-) protective; hypo (-lipidemia and -tensive) have been found in reported studies, but clinical studies are limited. CM is rich in polyphenols, vitamin C and minerals, resulting in it being a "superfood". Large-population and long-term clinical studies are needed to evaluate the biological activities of CM.

Abbreviations: CM, *cornus mas* L.; m, meter; mm, millimetre; g, gram; K, potassium; P, phosphorus; Ca, calcium; Mg, magnesium; Fe, iron; Cu, copper; Zn, zinc; Mn, manganese; Na, sodium; Al, aluminum; Si, silicon; S, sulphur; CI, chlorine; Cr, chrome; N, nickel; N, nitrogen; As, arsenic; B, boron; Ba, barium; Li, lithium; Se, selenium; Sr, strontium; V, vanadium; Ag, argent; Bi, bismuth; Cd, cadmium; Co, cobalt; Ga, gallium; Pb, plumbum; GA, gallic acid; fw, fresh weight; mg, milligram; GAE, gallic acid equivalents; dw, dried weight; CAT, catechin; mL, millilter; HPLC, High performance liquid chromatography; DAD, diode-array detector; UHPLC, ultra high performance liquid chromatography; HPTLC, high-performance thin-layer chromatography; LC-MS/MS, high-performance liquid chromatography coupled with tandem mass spectrometry; GC–MS, gas chromatograph-mass spectrometer; PDA, photometric diode array; UPLC-qTOF-MS/MS, ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry; ESI-TOF-MS, electrospray ionisation time-of-flight mass spectrometry; QE, quercetin equivalents; RU, rutin equivalents; n-6, omega-6; n-3, omega-3; DRI, dietary reference intake; ICP-AES, inductively coupled plasma atomic emission spectroscopy; Q-ICP-MS, quadrupole mass analyzer-single collector; DPPH, 1,1-diphenyl-2-picryl-hydrazyl radical inhibition test; FRAP, the ferric-reducing antioxidant properties method; ABTS, 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) radical cation; O_2-ARP, oxygen anti-radical power; TOAC, total antioxidant Capacity; CURRAP, copper reducing antioxidant capacity; ACI, antioxidant capacity of the liposoluble; EC_{50}, efficient concentration; RC_{50}, 50% reduction capacity; MOD, membrane osmotic distillation; PBS, phosphate buffer saline; A549, lung non small cell cancer; MCF-7, breast adenocarcinoma; SKOV3, ovarian cancer; PC-3, prostate adenocarcinoma; HeLa, cervix adenocarcinoma; LS174, colon carcinoma cell lines; HepG2, human liver carcinoma cells; CT26, murine colorectal carcinoma cells; Caco2, human colon cancer cells; HT-29, Human colon cancer cells; HaCaT, human keratinocyte cell lines; A431, epidermoid carcinoma cell lines; HGF, human gingival fibroblasts; DOK, human caucasian dysplastic oral keratinocytes; ATCC and CCL-81, African green monkey kidney epithelial cells-Vero; PL, AuNPs-CM, gold nanoparticles with water extract of CM fruits; AuNPs, gold nanoparticles; AgNPs, silver nanoparticles, pancreatic lipase; DM, diabetes mellitus; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; TG, total triglyceride; TC, total cholesterol; VLDL, very low-density lipoprotein; LDL, low-densitiy lipoprotein; HDL, high-density lipoprotein; FBG, fasting plasma glucose; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; *i.p.*, intraperitoneal injection; AST, aspartate transaminase; ALP, alkaline phosphatase; ALT, alanine transaminase; HSL, hormone-sensitive lipase; PPAR-α, peroxisome proliferator-activated receptor-α; PPAR-γ, peroxisome proliferator-activated receptor-γ; CCDP, dried powder of CM fruits; HFD, high fat diet; MDA, malondialdehyde; GPx, glutathione peroxidase; GSH, glutathione reductase; XO, xanthine oxidase; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; ADMA, asymmetric dimethyl arginine; DDAH, dimethylarginine dimethylaminohydrolase; SDMA, symmetric dimethylarginine; SOD, superoxide dismutase; TAM, Thrive Adaptogenics Max; AGE, advanced glycation end-products; AECM, acetone extract of CM fruits; IL-1β, interleukin-1β; IL-13, interleukin-13, IL-10, interleukin-10, MCP-1, monocyte chemoattractant protein-1; ERK ½, p44/42MAP Kinase; GGT, gamma-glutamyl transferase; PON1, paraoxonase 1; TAC, total antioxidant capacity; LWDHF, Liu-Wei-Di-Huang-Fang; MAP, mean arterial pressure; IOP, intraocular pressure; CT26, colon cancer cells; Apo B, apolipoprotein B; ICAM-1, intracellular adhesion molecule-1; VCAM-1, vascular cell adhesion protein-1; Apo A1, apolipoprotein A1; BMI, body mass index; CK-18 M30, Cytokeratin 18-M30

* Corresponding author.
E-mail addresses: merve.bayrm@gmail.com (H.M. Bayram), turkcana@hotmail.com (S. Arda Ozturkcan).

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1. Introduction

In recent years, there is a consensus that nutrition plays an important role in preventing many diseases. Consequently, healthy lifestyles, healthy diets and the use of medicinal plants has become increasingly popular. The genus *Cornus* is a member of the Cornaceae family, which include about 65 species, that are mostly trees and shrubs (Czerwinska & Melzig, 2018; Dinda et al., 2016). The genus *Cornus* (commonly referred to as dogwood), due to their hard woody stem, grows in Eurasia, North America, Northern South America, and Sub-Saharan Eastern Africa (Atkinson, Stockey, & Rothwell, 2016). The cornelian cherry, also known as *Cornus mas* L. (CM), is of the species of dogwood that is grown in Turkey, Romania, Bulgaria, Italy in Southern Europe and Southwest Asia (Czerwinska & Melzig, 2018; Dinda et al., 2016). The fruits, flowers, leaves, seeds and barks of CM, have been cultivated for nearly 400 years, and have been used in folk medicine since ancient times, especially in Asia (Kazimierski, Regula, & Molska, 2019).

CM is a photophilous plant with a small bloom and fruit found in shady areas. It can also be found in mountains up to 1400 m above sea level. It grows slowly and can live up to 300 years and is very resistant to drought and frost (Kazimierski et al., 2019). CM can adapt well to adverse environmental conditions and is diseases and pest resistant. In Turkey the average annual production of CM is reported to be approximately 11 tons (Turkish Statistical Institute, TUIK, 2019). The length of the plant trees is around 5-8 m. Its leaves are dark green, both sides are hairy, and the veins are parallel. CM generally bears small yellow flowers with red and elliptical fruits, but yellow or black fruits can also be seen (Ersoy, Kalyoncu, Citil, & Yilmaz, 2019; Szczepaniak, Kobus-Cisowska, Kusek, & Przeor, 2019a). It blooms fruit in September and October (Ersoy et al., 2019). The length of the fruits are 10–23 mm and weight from 1 to 10 g, while the seed weight in a range of 0.19–0.59 g (Bijelić, Gološin, Todorović, Cerović, & Bogdanović, 2012; Hassanpour, Hamidoghli, & Samizadeh, 2012; Moradi, Khadivi, & Salehi-Arjmand, 2019; Szot, Lipa, & Sosnowska, 2019; Yilmaz et al., 2009b).

CM can be a purposive food for the food industry (Kazimierski et al., 2019) and is used to produce different drinks, syrups, gels, jams and other traditional products (Dinda et al., 2016). In Bulgaria, CM fruits are consumed fresh, dried as a decoction, or made into a marmalade (Petkova & Ognyanov, 2018). In Turkey, it is used in traditional foods such as pestil and tarhana (Isik, Celik, & Yilmaz, 2014). Liquor, wine and puree of CM fruits are also produced in several countries (Adamenko, Kawa-Rygielska, Kucharska, & Piórecki, 2018; Nawirska-Olszańska, Biesiada, Kucharska, & Sokół-Łętowska, 2011; Petkova & Ognyanov, 2018; Tarko et al., 2014).

The use of CM as a medicinal plant took root between 450 and 100 BCE (Lietava et al., 2019). The plant is widely used in folk medicine for the treatment and prevention of diarrhea, hemorrhoids, diabetes, sore throat, digestive ailments, measles, chicken pox, anemia, rickets, liver and renal diseases (Dinda et al., 2016; Isik et al., 2014). Although there are review articles about CM in the literature, there is no article that presents detailed data together with the bioactive components and their analysis methods, and biological properties have not been thoroughly evaluated. The aim of this review is to present the bioactive components, biological and therapeutic effects of fruits, leaves, seeds and barks of CM, while providing an overview of its practicality in the pharmaceutical industry and as a nutritional supplement in the food industry.

2. Materials and methods

The literature search was mainly focused on chemical composition and bioactive components of CM, in addition to *in vitro*, *in vivo* and human clinical studies that used whole CM, juice, lyophilized (freeze-dried), compounds directly isolated from CM, different extracts of CM and nanotechnology and nanomaterials prepared with CM extract. When the keywords “cornelian cherry”, “*Cornus mas* L.”, “*C. mas*” used for search in Scopus, Elsevier, PubMed, Google scholar, a total of 255 articles were found spanning the period from 1998 till the end of 2019. Keywords for inclusion criteria: “chemical composition”, “bioactive components”, “polyphenols”, “phenolic acids”, “tannins”, “anthocyanins”, “flavonoids”, “flavanols”, “iridoids”, “triterpenoids”, “monoterpenoids”, “organic acids”, “carotenoids”, “carbohydrates”, “fatty acids”, “minerals”, “vitamin C”, “ascorbic acid”, “antioxidant”, “antimicrobial”, “cytotoxic”, “renal protective”, “liver protective”, “kidney protective”, “neuroprotective”, “hypolipidemic”, “anti-diabetic”, “anti-obesity”, “cardioprotective”, “anti-inflammatory”, “anti-hypertensive”, “anti-glaucoma”, “toxicity”, “nanomaterials”, “nanotechnology” and other related terms. According to included criteria 145 articles included in this review. This review analyzes the bioactive components of CM and its biological properties.

3. Bioactive components of *Cornus mas* L.

Studies have found an abundance of bioactive components such as organic molecules, carbohydrates, fatty acids, vitamins and minerals (Tables 1 and 2). The organic molecules in CM can be divided into five structural groups: anthocyanins, iridoids, phenolic acids, flavonoids, and tannins (Szczepaniak et al., 2019a). The quantity of these components depend on the plant genotype, cultivation, plant growth condition and the ripeness of the fruit (Dinda et al., 2016; Szczepaniak et al., 2019a). Usage methods are also discussed by the authors (Szczepaniak et al., 2019a).

The total amount of polyphenolic components of CM fruits are 45.6 mg gallic acid (GA)/g fresh weight (fw), which contain higher polyphenol levels compared to apple, pear and plum fruits (Gastol, Krośniak, Derwisz, & Dobrowolska-Iwanek, 2013). Antolak et al. (2017) found that CM fruits contain 2.33 ± 0.013 mg gallic acid equivalents (GAE)/g fw polyphenols. In a study by Okan, Serencam, Baltas, and Can (2019) the total polyphenols are 19.87 ± 0.27 mg GAE/g dry weight (dw) in CM fruits. Kucharska, Sokól-Łetowska, and Piórecki (2011) evaluated that the total amount of polyphenols are 4.64 mg/g fw for Szafer cultivars and 2.62 mg/g fw for Juliusz cultivars. The study suggested polyphenol levels are dependent on the cultivars. Cetkovská, Diviš, Vespalcová, Porízka, and Rezníček (2015) analyzed 9 cultivars of CM fruits and noted that the amount of polyphenols is between 2.17 ± 0.08 mg/g fw and 6.14 ± 0.2 mg/g fw. These findings are consistent with Sengul et al. and De Biaggi et al. studies. Sengul, Eser, and Ercisli (2014) analyzed 5 different genotypes of CM fruits and found that the total amount of polyphenol components ranges from 6.53 to 10.09 mg GAE/g fw. De Biaggi et al. (2018) found that “Chieri” genotypes of CM fruits showed the highest amount of polyphenols with 1.97 ± 0.25 mg GAE/g fw. A study by Gunduz, Saracoglu, Ozgen, and Serce (2013) stated that the total amount of polyphenolic components depends on the maturity of fruits. In their study, the red CM fruits contain the lowest amount of polyphenols (4.162 mg GAE/g fw), whereas the yellow CM fruits contain the highest amount of polyphenols (8.206 mg GAE/g fw). With the exception of CM fruits, total polyphenols are found highest in the leaves of CM with values of 101.402 mg GAE/g dw (Taktak & Ilbay, 2016).

The total polyphenols of CM in different extract solutions have also been studied. Tarko et al. (2017b) found water and methylene chloride solutions are not suitable for evaluating the total polyphenols, however 80% methanol solution showed the highest results. The total amount of polyphenols was 16.36 ± 0.37 mg/g fw in 80% methanol solution, 10.33 ± 0.38 mg/g fw in 80% ethanol solution, 4.63 ± 0.47 mg/g fw in water solution and 0.07 ± 0.00 mg/g fw in methylene chloride solution. Similarly, in a study conducted by Szczepaniak et al. (2019b) the total polyphenols of the ethanol and water extracts of CM fruits range from (mg GAE/g dw) 25.98 ± 4.76 to 5.50 ± 0.66; and 7.75 ± 0.13 to 2.90 ± 0.01, respectively. However, the value of these

Table 1
Bioactive components of *Cornus mas* L.

Phytochemical group	Chemical components
Anthocyanins	Cyanidin 3-O-glucoside (Seeram et al., 2002; Tural & Koca, 2008; Antolak et al., 2017), cyanidin 3-O-robinobioside (Antolak et al., 2017; Dzydzan et al., 2019; Kucharska et al., 2015; Sozański et al., 2014; Szumny et al., 2015), cyanidin 3-O-rutinoside (Capanoglu et al., 2011; Tural & Koca, 2008; Sengul et al., 2014; Tarko et al., 2017b), pelargonidin 3-O-galactoside (Jayaprakasam et al., 2006; Sozański et al., 2014; Kucharska et al., 2015; Perova et al., 2014; Szumny et al., 2015; Dzydzan et al., 2019; Ochmian et al., 2019; Świerczewska et al., 2019) pelargonidin 3-O-glucoside (Seeram et al., 2002; Tural & Koca, 2008; Antolak et al., 2017), pelargonidin 3-O-robinobioside (Antolak et al., 2017; Dzydzan et al., 2019; Kucharska et al., 2015; Sozański et al., 2014; Szumny et al., 2015), pelargonidin 3-O-rutinoside (Pawlowska et al., 2010), peonidin-3-O-glucoside (Begic-Akagic et al., 2013; Drkenda et al., 2014; Sengul et al., 2014), delphinidin-3-O-galactoside (Kucharska et al., 2015; Sozański et al., 2014), delphinidin 3-O-β-glucoside (Seeram et al., 2002), petunidin 3-glucoside (Antolak et al., 2017)
flavanoids	Quercetin (Sochor et al., 2014), quercetin 3-O-robinobioside (Begic-Akagic et al., 2013; Drkenda et al., 2014), quercetin 3-O-glucuronide (Moldovan et al., 2016a; Bajić-Ljubičić et al., 2018; Popović et al., 2018; Dzydzan et al., 2019), quercetin-3-O-xyloside (Pawlowska et al., 2010; Drkenda et al., 2014), quercetin-3-O-rhamnoside (Pawlowska et al.,2010; Begic-Akagic et al., 2013; Drkenda et al., 2014; Sochor et al., 2014), quercetin-3-O-glucoside (Pawlowska et al., 2010; Begic-Akagic et al., 2013; Drkenda et al., 2014; Milenković-Andjelković et al., 2015; Antolak et al., 2017), quercetin-3-O-galactoside (Pawlowska et al., 2010; Begic-Akagic et al., 2013; Drkenda et al., 2014), kaempferol 3-O-galactoside (Pawlowska et al., 2010), kaempferol 3-glucoside (Begic-Akagic et al., 2013; Drkenda et al., 2014; Milenković-Andjelković et al., 2015), myricetin (Cosmulescu et al., 2019, 2017), myricetin 3-galactoside (Antolak et al., 2017), aromadendrin (Pawlowska et al., 2010)
Flavonols	Procyanidin B1 (Begic-Akagic et al., 2013; Drkenda et al., 2014), procyanidin B2 (Drkenda et al., 2014), (+) catechin (Milenković-Andjelković et al., 2015), (−) epicatechin (Capanoglu et al., 2011; De Biaggi et al., 2018; Moldovan et al., 2016a)
Phenolic acids and tannins	Gallic acid (Cosmulescu et al., 2019; Natić et al., 2019; Okan et al., 2019), ellagic acid (Moldovan et al., 2016a; De Biaggi et al., 2018; Natić et al., 2019), chlorogenic acid (Deng et al., 2013; Drkenda et al., 2014; Sochor et al., 2014), neochlorogenic acid (Bajić-Ljubičić et al., 2018), 3-O-caffeoylquinic acid (Dzydzan et al., 2019; Natić et al., 2019), p-coumaric acid (Cosmulescu et al., 2019), caffeic acid (Cosmulescu et al., 2017), protocatechuic acid (Antolak et al., 2017), benzoic acid (Krivoruchko, 2014), cinnamic acid (Antolak et al., 2017; Cosmulescu et al., 2017), ferulic acid (Antolak et al., 2017; Cosmulescu et al., 2017; Krivoruchko, 2014), sinapic acid (Cosmulescu et al., 2017), salicylic acid (Cosmulescu et al., 2017; Krivoruchko, 2014), syringinc acid (Cosmulescu et al., 2017), vanillic acid Krivoruchko, 2014; Cosmulescu et al., 2017), rosmarinic acid (Antolak et al., 2017)
Iridoids	Loganic acid (Dzydzan et al., 2019; Kawa-Rygielska et al., 2019; Kucharska et al., 2015; Perova et al., 2014; Sozański et al., 2014; Świerczewska et al., 2019; Szumny et al., 2015; West et al., 2012a), loganin (Perova et al., 2014), cornuside (Deng et al., 2013; Dzydzan et al., 2019; Kucharska et al., 2015; Perova et al., 2014; Sozański et al., 2014; Szumny et al., 2015), sweroside (Deng et al., 2013; Perova et al., 2014), catalposide (Sochor et al., 2014), catalposide (Sochor et al., 2014)
Triterpenoids	Ursolic acid (Jayaprakasam et al., 2006)
Monoterpenoids	Limonene (De Biaggi et al., 2018)
Carbohydrates	Glucose (Okan et al., 2019; Petkova & Ognyanov, 2018; Tarko et al., 2015), sucrose (Bijelić et al., 2011; Jaćimović et al., 2015; Okan et al., 2019; Petkova & Ognyanov, 2018), fructose (Okan et al., 2019; Tarko et al., 2015)
Organic acids	Malic acid (De Biaggi et al., 2018; Drkenda et al., 2014), citric acid (De Biaggi et al., 2018; Drkenda et al., 2014; Sochor et al., 2014), tartaric acid (De Biaggi et al., 2018; Drkenda et al., 2014)
Fatty acids	Linoleic acid (Brindza et al., 2009; Kazimierski et al., 2019; Krivoruchko, 2014; Tiptiri-Kourpeti et al., 2019), oleic acid (Brindza et al., 2009; Kazimierski et al., 2019; Krivoruchko, 2014), α-linolenic acid (Brindza et al., 2009; Kazimierski et al., 2019; Krivoruchko, 2014), palmitoleic acid (Brindza et al., 2009; Krivoruchko, 2014), palmitic acid (Brindza et al., 2009; Kazimierski et al., 2019; Krivoruchko, 2014), stearic acid (Kazimierski et al., 2019), behenic acid (Krivoruchko, 2014), lauric acid (Brindza et al., 2009; Krivoruchko, 2014), myristic acid (Brindza et al., 2009), pentadecenic acid (Brindza et al., 2009), pentaddecanoic acid (Krivoruchko, 2014)
Carotenoids (Horváth, Turcsi, Molnar, Szabo, & Deli, 2007)	(13Z) + (13′Z)-Lutein, (9Z) + (9′Z)-Lutein, (9′Z)-Neoxanthin, (E)-Neoxanthin, Lutein-5,6-epoxide, Luteoxanthin (epimers), Neochrome (epimers), β-carotene), β-carotene-5,6-monoepoxide, β-cryptoxanthin

components depend on the storage processes. For example, Moldovan, Popa, and David (2016b) found that the total polyphenol content in CM extracts show a rapid decrease at 75 °C, whereas stored at 2° and 22 °C cause a slight decrease.

Tarko et al. (2014) showed the total amount of polyphenols are 6.11 ± 0.08 mg/g fw catechin (CAT) equivalents in CM fruits, 0.75 ± 0.12 mg/mL CAT equivalents in CM wine and 1.54 ± 0.15 mg/mL CAT equivalents in CM liqueur. They also noted that the seeds and barks of CM include about 90% of polyphenols of all the different parts of CM (Tarko et al., 2014). Studies show that not only the fruits of CM, but also the barks, leaves and seeds of CM are rich in polyphenols, which can make this plant a functional food.

3.1. Phenolic acids and tannins

The reported phenolic acids in CM fruits are gallic acid (Cosmulescu, Trandafir, & Cornescu, 2019; Natić et al., 2019; Okan et al., 2019), ellagic acid (De Biaggi et al., 2018; Moldovan et al., 2016a; Natić et al., 2019), chlorogenic acid (Deng, West, & Jensen, 2013; Drkenda et al., 2014; Sochor et al., 2014), neochlorogenic acid (Bajić-Ljubičić, Popović, Matić, & Bojović, 2018), 3-O-caffeoylquinic acid (Dzydzan, Bila, Kucharska, Brodyak, & Sybirna, 2019; Natić et al., 2019), p-coumaric acid (Cosmulescu et al., 2019), caffeic acid (Cosmulescu, Trandafir, & Nour, 2017), protocatechuic acid (Antolak et al., 2017), benzoic acid (Krivoruchko, 2014), cinnamic acid (Antolak et al., 2017; Cosmulescu et al., 2017), ferulic acid (Antolak et al., 2017; Cosmulescu et al., 2017; Krivoruchko, 2014), sinapic acid (Cosmulescu et al., 2017), salicylic acid (Cosmulescu et al., 2017; Krivoruchko, 2014), syringinc acid (Cosmulescu et al., 2017), vanillic acid (Cosmulescu et al., 2017; Krivoruchko, 2014) and rosmarinic acid (Antolak et al., 2017). These were determined using the following methods: High performance liquid chromatography (HPLC) (Cosmulescu et al., 2017; Okan et al., 2019; Sochor et al., 2014), HPLC with a diode-array detector (DAD) (Antolak et al., 2017; De Biaggi et al., 2018; Drkenda et al., 2014; Dzydzan et al., 2019), Ultrahigh performance liquid chromatography (UHPLC) (Cosmulescu et al., 2019; Deng et al., 2013; Dzydzan et al., 2019), UHPLC-DAD (Natić et al., 2019), High-performance thin-layer chromatography (HPTLC) (Moldovan et al., 2016a), High-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) (Antolak et al.,

Table 2
Total amount of organic molecules of *Cornus mas* L.

Phenolic acids	Anthocyanins	Tannins	Flavonoids	Flavanols	Iridoids	Part of CM	Country	References
2.81–5.79 mg/g mL methanol extr. of fw	1.12–2.92 mg/g mL methanol extr. of fw					Fruits	Turkey	Tural & Koca, 2008
29.76–74.83 mg/GAE/g methanol extr. of dw	148–237 mg/100 g methanol extr. of fw					Fruits	Turkey	Yilmaz et al., 2009a
		129.503 ± 2.296 mg/100 g fw				Fruits	Turkey	Kalyoncu et al., 2009
		0.57–1.28% fw				Fruits	Turkey	Ercisli et al., 2011
	35.63–126.53 mg/100 g fw	0.56–1.47% fw				Fruits	Serbia	Bijelić et al., 2011
1097.19–2695.75 mg GAE/100 g methanol extr. of fw	191.87–442.11 mg/100 g methanol extr. of fw		321.27–669 mg CAT/100 g methanol extr. of fw			Fruits	Iran	Hassanpour et al., 2011
4918.8 ± 195.7 mg GAE/100 g water extr. of dw			477.3 ± 22.9 mg CE/100 g water extr. of dw			Fruits	Turkey	Capanoglu et al., 2011
31.25 ± 1.79 mg GAE/g water extr. of dw	229 ± 16.9 mg EGCC-E/g water extr. of dw		20.5 ± 1.62 mg QE/g water extr. of dw			Fruits	Turkey	Celep et al., 2012
494–704 mg GAE/100 g water extr. of dw	0.058–3.029 mg CG/g water extr. of dw					Fruits	Serbia	Popović et al., 2012
150–400 mg/100 g ethanol extr. of fw	11.2–92.2 mg/100 g ethanol extr. of fw					Fruits	Russia	Perova et al., 2014
6.53–10.09 μg GAE/mg ethanol extr. of fw	239–342 mg/100 mL methanol extr. of fw					Fruits	Turkey	Sengul et al., 2014
2174 ± 77–6143 ± 195 mg/kg water extr. of fw	61 ± 7–347 ± 4 mg/kg water extr. of fw					Fruits	Czech Republic	Cetkovská et al., 2015
489.94 ± 17.88 mg/100 g acetone extr. of fw	92.23 ± 2.03 mg cy-3-glu/100 g acetone extr. of fw			66.89 mg/100 g epicatechin acetone extr. of fw		Fruits	Romania	Moldovan et al., 2016a
196.68 ± 24.68 mg GAE/ 100 g fw	134.71 ± 7.10 mg cy-3-glu /100 g fw					Fruits	Italy	De Biaggi et al., 2018
	98.0–290.3 mg cy-3-glu /100 g sodium borate extr. of fresh pomace					Fruits	Poland	Szot et al., 2019
	215.46–232.25 mg/100 g water extr. of dw		9.63–10.10 mg/100 g water extr. of dw			Fruits	Poland	Ochmian et al., 2019
266.65 ± 6.84 mg GAE/100 g methanol extr. of fw			33.97 ± 1.74 mg QE/100 g methanol extr. of fw			Fruits	Romania	Cosmulescu et al., 2019
19.87 ± 0.27 mg GAE/g methanol extr. of dw			0.59 ± 0.01 mg QE/g methanol extr. of dw			Fruits	Turkey	Okan et al., 2019
657–2611 mg GAE/100 g methanol extr. of fw	1.3–223 mg cy-3-glu/100 g acetate extr. of fw					Yellow fruits	Greece	Pantelidis et al., 2007
	5.59–341.18 mg/100 g methanol extr. of fw				86.91–493.69 mg/100 g methanol extr. of fw	Red fruits	Poland	Kucharska et al., 2015
	4.9 μg cy-3-glu/g acetone extr. of fw					Light yellow fruits	Turkey	Gunduz et al., 2013
	16.5 μg cy-3-glu/g acetone extr. of fw					Yellow fruits		
	65.8 μg cy-3-glu/g acetone extr. of fw					Light red fruits		
	65.0 μg cy-3-glu/g acetone extr. of fw					Dark red fruits		
2157.17 mg/100 g ethanol extr. of dw					20303.75 mg/100 g ethanol extr. of dw	Yellow fruits	Poland	Dzydzan et al., 2019

(*continued on next page*)

Table 2 (*continued*)

Phenolic acids	Anthocyanins	Tannins	Flavonoids	Flavanols	Iridoids	Part of CM	Country	References
1285.52 mg/100 g ethanol extr. of dw	2066.80 mg/100 g ethanol extr. of dw				14068.98 mg/100 g ethanol extr. of dw	Red fruits		
	181.7 ± 6.9 mg GAE/g methanol extr. of dw		10.5 ± 0.7% dw				Flowers	Serbia
Šavikin et al., 2009	56.9 ± 3.2 mg GAE/g methanol extr. of dw		1.61 ± 0.1% dw				Leaves	
89.89 ± 0.45–91.12 ± 0.59 mg/g methanol/acetone/water/formic acid (30/42/27.5/0.5) extr. of dw	15.5 ± 0.18–16.1 ± 0.27 mg/g methanol/acetone/water/formic acid (30/42/27.5/0.5) extr. of dw					Fruits	Serbia	Milenković-Andjelković et al., 2015
112.91 ± 1.40–117.34 ± 1.40 mg/g methanol/acetone/water/formic acid (30/42/27.5/0.5)extr. of dw						Leaves		
2979.25 ± 69.40 mg GAE/100 g fw			255.75 ± 14.92 QE/100 g fw			Acetone extr. of fruits	Turkey	Karaaslan et al., 2018
721.86 ± 28.72 mg GAE/100 g fw			255.75 ± 14.92 QE/100 g fw			Acetonitrile extr. of fruits		
2006.33 ± 31.94 mg GAE/100 g fw			76.01 ± 2.61 QE/100 g fw			Ethanol extr. of fruits		
2006.33 ± 31.94 mg GAE/100 g fw			80.54 ± 4.71 QE/100 g fw			Methanol extr. of fruits		
439.85 ± 34.57 mg GAE/10 0 g fw			28.57 ± 0.91 mg QE/100 g fw			Water extr. of fruits		
131.5 ± 0.3 mg GAE/g dw			0.07 ± 0.01% dw			70% methanol extr. of fruits	Iran	Abbasi et al., 2020
342.6 ± 10.7 mg GAE/g dw			72.83 ± 3.1 mg QE/g dw			80% methanol extr. of leaves	Turkey	Celep et al., 2013
65.13 ± 0.72 mg GA/g (ethyl acetate extr.)-341.09 ± 0.46 mg/GA/g (water extr.) dw			22.18 ± 0.58 (water extr.)-149.97 ± 0.81 mg RU/g (ethyl acetate extr.) dw			Leaves	Serbia	Stankovic et al., 2014
31.52 ± 0.45 mg/GA/g (petroleum ether extr.)-187.94 ± 1.49 mg GA/g (methanol extr.) dw			47.23 ± 0.30 (water extr.)-55.70 ± 0.21 mg RU/g (ethyl acetate extr.) dw			Flowers		
27.14 ± 0.33 mg GA/g (petroleum ether extr.)-179.05 ± 0.53 mg GA/g (ethyl acetate extr.) dw			3.53 ± 0.39 (water extr.)-41.49 ± 0.57 mg RU/g (ethyl acetate extr.) dw			Fruits		

fw, fresh weight; dw, dry weight; mg, milligram; g, gram; mL, milliliter; GA, gallic acid; GAE, gallic acid equivalents; CAT, catechin; CE, (+) catechin and (−) epicatechin; EGCC-E, epigallocatechin gallate equivalents; QE, quercetin equivalents; CG-Cyanidin-3-glucoside equivalents; cy-3-glu, cyanidin-3-glucose; RU, rutin equivalents.

2017; Bajić-Ljubičić et al., 2018) and Gas chromatograph-mass spectrometer (GC–MS) (Krivoruchko, 2014).

The Folin–Ciocalteu method is the most used method to evaluate total phenolics (Antolak et al., 2017; Capanoglu, Boyacioglu, De Vos, Hall, & Beekwilder, 2011; Celep, Aydin, & Yesilada, 2012; Cetkovská et al., 2015; Cosmulescu et al., 2019, 2017; De Biaggi et al., 2018; Gąstoł et al., 2013; Hassanpour, Yousef, Jafar, & Mohammad, 2011; Koca, 2008; Moldovan et al., 2016a; Natić et al., 2019; Okan et al., 2019; Pantelidis, Vasilakakis, Manganaris, & Diamantidis, 2007; Perova et al., 2014; Popović, Štajner, Slavko, & Sandra, 2012; Šavikin et al., 2009; Sengul et al., 2014; Taktak & Ilbay, 2016; Tarko et al., 2014, 2017b; Tural & Koca, 2008; Yilmaz, Ercisli, Zengin, Sengul, & Kafkas, 2009a) followed by spectrophotometric method (Milenković-Andjelković, Andjelković, Radovanović, Radovanović, & Nikolić, 2015) and the procedure of Singleton and Rossi (1965) (Gunduz et al., 2013). Total phenolic acids ranged from 1.8 to 5 mg/GAE/g dw in Turkey (Capanoglu et al., 2011; Celep et al., 2012; Yilmaz et al., 2009a); 4.94 to 7.04 mg/GA/g dw in Serbia (Popović et al., 2012); 2.67 ± 0.68 mg GAE/g fw in Romania (Cosmulescu et al., 2019); 10.97 to 26.96 mg GAE/g fw in Iran (Hassanpour et al., 2011) and 6.57 to 26.11 mg GAE/g fw in Greece (Pantelidis et al., 2007); 1.5 to 4 mg/g fw in Russia (Perova et al., 2014).

Dzydzan et al. (2019) showed that the difference in the total amount of phenolic acids is related to the cultivar and color of fruit. They found total phenolic acid levels are 21.57 mg/g dw in yellow CM fruits, and 12.86 mg/g dw in red CM fruits. Moreover, the total phenolic acids of leaves are higher than the fruits of CM. These amount ranged from 112.91 ± 1.40 to 117.34 ± 1.40 mg/g dw in leaves, compared to 89.89 ± 0.45 to 91.12 ± 0.59 mg/g dw in fruits (Milenković-Andjelković et al., 2015).

Limited studies have determined the total tannin contents. Tannin content was determined by the procedure of Horwitz (1975) (Kalyoncu, Ersoy, & Yilmaz, 2009), Vračar (2001) (Bijelić, Gološin, Todorović, Cerović, & Popović, 2011) and AOAC (1995) (Ercisli et al., 2011); and an indirect determination, its adsorption on standard hide powder (Šavikin et al., 2009). Kalyoncu et al. (2009) showed that the total amount of tannin was 129.503 ± 2.296 mg/100 g fw. Ercisli et al. (2011) found that the percentage of tannin ranged from 0.57% to 1.28% fw. However, Bijelić et al. (2011) reported a range of 0.56–1.47% fw. Additionally, total tannin was 10.5 ± 0.7% dw in the flowers of CM, whereas 1.61 ± 0.1% dw in the leaves (Šavikin et al., 2009).

3.2. Anthocyanins

Anthocyanins are different components of CM fruits (Szczepaniak et al., 2019a). The prevalent anthocyanins in CM fruits are cyanidin 3-O-glucoside (Antolak et al., 2017; Seeram, Schutzki, Chandra, & Nair, 2002; Tural & Koca, 2008), cyanidin 3-O-robinobioside (Antolak et al., 2017; Dzydzan et al., 2019; Kucharska, Szumny, Sokół-Letowska, Piórecki, & Klymenko, 2015; Sozański et al., 2014; Szumny et al., 2015), cyanidin 3-O-rutinoside (Capanoglu et al., 2011; Sengul et al., 2014; Tarko et al., 2017b; Tural & Koca, 2008), peonidin-3-O-glucoside (Begic-Akagic, Drkenda, Vranac, Orazem, & Hudina, 2013; Drkenda et al., 2014; Sengul et al., 2014), pelargonidin 3-O-glucoside (Antolak et al., 2017; Seeram et al., 2002; Tural & Koca, 2008), pelargonidin 3-O-robinobioside (Antolak et al., 2017; Dzydzan et al., 2019; Kucharska et al., 2015; Sozański et al., 2014; Szumny et al., 2015), pelargonidin 3-O-galactoside (Dzydzan et al., 2019; Jayaprakasam, Olson, Schutzki, Tai, & Nair, 2006; Kucharska et al., 2015; Ochmian, Oszmiański, Lachowicz, & Krupa-Małkiewicz, 2019; Perova et al., 2014; Sozański et al., 2014; Świerczewska, Buchholz, Melzig, & Czerwińska, 2019; Szumny et al., 2015), pelargonidin 3-O-rutinoside (Pawlowska, Camangi, & Braca, 2010), delphinidin-3-O-galactoside (Kucharska et al., 2015; Sozański et al., 2014), delphinidin 3-O-β-glucoside (Seeram et al., 2002) and petunidin 3-glucoside (Antolak et al., 2017). The following methods were used to identify anthocyanins: HPLC (Jayaprakasam et al., 2006; Seeram et al., 2002; Sengul et al., 2014; Tarko et al., 2017b; Tural & Koca, 2008), HPLC-DAD (Antolak et al., 2017; Begic-Akagic et al., 2013; Drkenda et al., 2014; Dzydzan et al., 2019), HPLC-DAD-mass spectrometry (MS) (Świerczewska et al., 2019), HPLC- Photometric diode array (PDA) (Capanoglu et al., 2011; Kucharska et al., 2015), Ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-qTOF-MS/MS) (Kucharska et al., 2015; Sozański et al., 2014); UHPLC (Ochmian et al., 2019; Szumny et al., 2015), HPLC with UV and Electrospray ionisation time-of-flight mass spectrometry (ESI-TOF-MS) (Perova et al., 2014), HPLC–PDA–ESI-MS (Pawlowska et al., 2010) and LC-MS (Antolak et al., 2017).

The methods used to determine the total amount of anthocyanins differ according to the literature. The most used methods are the pH-differential spectrophotometric method (Cetkovská et al., 2015; De Biaggi et al., 2018; Gunduz et al., 2013; Hassanpour et al., 2011; Koca, 2008; Milenković-Andjelković et al., 2015; Moldovan et al., 2016a; Pantelidis et al., 2007; Perova et al., 2014; Popović et al., 2012; Tural & Koca, 2008; Yilmaz et al., 2009a) and a procedure described by Chandra, Rana, and Li (2001) (Sengul et al., 2014). The amount of anthocyanins in CM varies according the country where it is grown. The total anthocyanins range from 0.12 to 4.2 mg/g fw in Turkey (Koca, 2008; Sengul et al., 2014; Tural & Koca, 2008; Yilmaz et al., 2009a), 0.36 mg/g to 1.27 fw in Serbia (Bijelić et al., 2011), 0.061 ± 0.007 to 0.347 ± 0.004 mg/g fw in Czech Republic (Cetkovská et al., 2015), 0.05 to 3.42 mg/g fw in Poland (Kucharska et al., 2015; Ochmian et al., 2019), 1.92 to 4.42 mg/g fw in Iran (Hassanpour et al., 2011) and 0.11–0.92 mg/g fw in Russia (Perova et al., 2014).

Total anthocyanin levels are dependent upon the cultivar and the color of CM. Red CM fruits contain 20.67 mg/g dw anthocyanins, while yellow fruits do not (Dzydzan et al., 2019). However, Gunduz et al. (2013) showed that total anthocyanins differ according to the ripeness of the fruit and found that the mean amount of anthocyanins are 38 μg cyanidin-3-glucose (cy-3-glu)/g fw in all colors of CM fruits; 4.9 μg cy-3-glu/g fw in light yellow, 16.5 μg cy-3-glu/g fw in yellow, 65.8 μg cy-3-glu/g fw in light red and 65.0 μg cy-3-glu/g fw in the dark red fruits of CM. Additionally, anthocyanins depend on the storage temperature processes. The degradation rate of anthocyanins isolated from CM extracts was 1.8 times faster at 2° C, while the process was 172 times faster at 75 °C (Moldovan & David, 2014).

3.3. Flavonoids

The usage methods for determining flavonoid in literature are HPLC (Cosmulescu et al., 2017; Dzydzan et al., 2019; Milenković-Andjelković et al., 2015; Sochor et al., 2014), HPLC-DAD (Antolak et al., 2017; Begic-Akagic et al., 2013; Drkenda et al., 2014), HPLC-DAD-ESI-MS (Badalica-Petrescu, Dragan, Ranga, Fetea, & Socaciu, 2014), HPLC–PDA–ESI-MS (Pawlowska et al., 2010), LC-MS (Antolak et al., 2017), LC-MS/MS (Bajić-Ljubičić et al., 2018), UHPLC (Cosmulescu et al., 2019) and HPTLC (Moldovan et al., 2016a). In fruits, quercetin (Sochor et al., 2014), quercetin 3-O-robinobioside (Begic-Akagic et al., 2013; Drkenda et al., 2014), quercetin 3-O-glucuronide (Bajić-Ljubičić et al., 2018; Dzydzan et al., 2019; Moldovan et al., 2016a; Popović, Matić, Bajić-Ljubičić, Tešević, & Bojović, 2018), quercetin-3-O-xyloside (Drkenda et al., 2014; Pawlowska et al., 2010), quercetin-3-O- rhamnoside (Begic-Akagic et al., 2013; Drkenda et al., 2014; Pawlowska et al., 2010; Sochor et al., 2014), quercetin-3-O-glucoside (Antolak et al., 2017; Begic-Akagic et al., 2013; Drkenda et al., 2014; Milenković-Andjelković et al., 2015; Pawlowska et al., 2010), quercetin-3-O-galactoside (Begic-Akagic et al., 2013; Drkenda et al., 2014; Pawlowska et al., 2010), kaempferol 3-O-galactoside (Pawlowska et al., 2010), kaempferol 3-glucoside (Begic-Akagic et al., 2013; Drkenda et al., 2014; Milenković-Andjelković et al., 2015), myricetin (Cosmulescu et al., 2019, 2017), myricetin 3-galactoside (Antolak et al., 2017),

aromadendrin (Pawlowska et al., 2010) are found in fruits of CM whereas in the leaves, quercetin 3-O-glucuronide is the major flavonoid compound (Badalica-Petrescu et al., 2014).

Total flavonoids vary depending on the country of origin. Determination of total flavonoids were assessed with the aluminum nitrate colorimetric method (Celep et al., 2012; Cosmulescu et al., 2019, 2017), and a procedure described by Fukumoto and Mazza (2000) (Okan et al., 2019) and Dewanto, Wu, Adom, and Liu (2002) (Capanoglu et al., 2011). Total flavonoids range between 0.5 and 207 mg quercetin equivalents (QE)/g dw in Turkey (Celep et al., 2012; Okan et al., 2019); 3.21 and 6.69 mg CAT/g fw in Iran (Hassanpour et al., 2011); and 0.09 and 0.1 mg/g dw in Poland (Ochmian et al., 2019). The total amount of flavonoids varies according to different solutions. Karaaslan, Karaaslan, and Ates (2018) showed that acetone extract of CM fruits gives the highest total flavonoid contents. Abbasi et al. (2020) found the mean total flavonoids are 0.07 ± 0.01% dw in 70% methanol extract of CM fruits.

Additionally, flavonoids are the major components of CM leaves (Dinda et al., 2016). The total flavonoids found are 72.83 ± 3.1 mg QE/g dw in 80% methanol extract of CM leaves (Celep, Aydin, Kirmizibekmez, & Yesilada, 2013). Similarly, another study determined the total flavonoids range from 22.18 ± 0.58 (water extract) to 149.97 ± 0.81 mg rutin equivalents (RU)/g dw (ethyl acetate extract) in leaves (Stankovic, Zia-Ul-Haq, Bojovic, & Topuzovic, 2014).

3.4. Flavanols

The flavanols found in CM are: procyanidin B1 (Begic-Akagic et al., 2013; Drkenda et al., 2014), procyanidin B2 (Drkenda et al., 2014), (+) catechin (Milenković-Andjelković et al., 2015) and (−) epicatechin (Capanoglu et al., 2011; De Biaggi et al., 2018; Moldovan et al., 2016a) using HPLC (Milenković-Andjelković et al., 2015), HPLC-DAD (Begic-Akagic et al., 2013; De Biaggi et al., 2018; Drkenda et al., 2014), HPLC-PDA (Capanoglu et al., 2011) and HPTLC methods (Moldovan et al., 2016a). Epicatechin is the predominant flavanols in the fruits (Capanoglu et al., 2011; De Biaggi et al., 2018; Moldovan et al., 2016a), and a study showed that CM fruits are rich in procatechin (Antolak et al., 2017). According to HPTLC method Moldovan et al. (2016a) found the mean amount of flavanols are 0.67 mg/g fw epicatechin.

3.5. Iridoids

The studies about the following iridoids are presented in CM fruits: loganic acid (Dzydzan et al., 2019; Kawa-Rygielska, Adamenko, Kucharska, Prorok, & Piórecki, 2019; Kucharska et al., 2015; Perova et al., 2014; Sozański et al., 2014; Świerczewska et al., 2019; Szumny et al., 2015; West, Deng, Jensen, Palu, & Berrio, 2012a), loganin (Deng et al., 2013; Perova et al., 2014), cornuside (Deng et al., 2013; Dzydzan et al., 2019; Kucharska et al., 2015; Perova et al., 2014; Sozański et al., 2014; Szumny et al., 2015), sweroside (Deng et al., 2013; Perova et al., 2014), catalposide (Sochor et al., 2014). The identification methods used for iridoid components include HPLC (Sochor et al., 2014; West et al., 2012a), HPLC-DAD (Kawa-Rygielska et al., 2019; Szumny et al., 2015), HPLC-DAD-MS (Świerczewska et al., 2019), HPLC with UV and ESI-TOF-MS (Perova et al., 2014) and UPLC-qTOF-MS/MS (Dzydzan et al., 2019; Kucharska et al., 2015; Sozański et al., 2014).

Moreover, total iridoids were determined using the Acquity ultra-performance liquid chromatography (UPLC) system (Dzydzan et al., 2019; Kucharska et al., 2015). Total iridoids are between 0.87 and 4.94 mg/g (Kucharska et al., 2015). Also, Dzydzan et al. (2019) noted that the total amount of iridoids depend on cultivar and color of the fruit. In yellow CM, the total iridoids are 203.04 mg/g dw, whereas in red CM, 140.69 mg/g dw.

3.6. Triterpenoids and monoterpenoids

Ursolic acid, one of triterpenoids (Jayaprakasam et al., 2006), and limonene (the mean amount of 1.16 ± 0.01 mg/g fw), one of monoterpenoids, are reported using the HPLC-DAD method in the fruits and flowers of CM according to the literature (De Biaggi et al., 2018).

3.7. Organic acids

Malic acid, citric acid and tartaric acid are found in CM fruits using HPLC-DAD method (De Biaggi et al., 2018; Drkenda et al., 2014). Drkenda et al. (2014) showed that CM cultivars of Bosnia and Herzegovina contain malic acid (3.5–4.3% fw), followed by tartaric acid (0.11–0.28% fw) and citric acid (0.01–0.1% fw), whereas CM cultivars of Czech Republic are rich in citric acid (2.3% fw) (Sochor et al., 2014).

3.8. Carotenoids

Studies evaluating the amount of carotene in CM fruits are very limited. Carotene levels of 0.07 mg/g were identified in fresh CM fruits and 0.008 mg/g of carotene in dried CM fruits (Rosu et al., 2011).

3.9. Carbohydrates and pectin

Carbohydrates are important components for evaluating the quality of fruits in connection with the sugar content as a major parameter affecting the consumption of fruits. The total sugar contents of CM fruits range from 10.42 to 25.23% fw (Andronie et al., 2019; Bijelić et al., 2011; Jaćimović, Božović, Ercisli, Ognjanov, & Bosančić, 2015; Kawa-Rygielska et al., 2019; Rosu et al., 2011). Glucose is the dominant sugar (2.5–13%), followed by fructose (1.79–6% fw) (Antolak et al., 2017; Okan et al., 2019; Petkova & Ognyanov, 2018; Tarko et al., 2014) and sucrose (0.08–3.10% fw) (Bijelić et al., 2011; Jaćimović et al., 2015; Okan et al., 2019; Petkova & Ognyanov, 2018).

CM also contains pectin and calcium pectate which is a typical fiber (Bijelić et al., 2011; Dokoupil & Řezníček, 2012; Jaćimović et al., 2015; Sochor et al., 2014). Pectin content in CM is between 8.70 ± 0.39 mg/g fw and 15.00 ± 0.53 mg/g fw (Dokoupil & Řezníček, 2012; Sochor et al., 2014). Bijelić et al. (2011) and Jaćimović et al. (2015) found that the percentage of calcium pectate ranged from 0.37 to 2.4% fw. This would allow CM to be used in the canning industry as a fermentation substrate.

3.10. Fatty acids

CM fruits contain 4 mg/g dw of lipids (Andronie et al., 2019). Horvarth et al., reported ten fatty acids of high concentration in the fruits and leaves of CM (Czerwinska & Melzig, 2018). The highest amount of fatty acid, linoleic acid ranged from 73.3 to 76.7% fw (Brindza, Brindza, Tóth, Klimenko, & Grigorieva, 2009; Ersoy et al., 2019; Kazimierski et al., 2019), followed by oleic acid with 17.1% fw (Kazimierski et al., 2019). Similarly, the most abundant fatty acid in the barks and seeds of CM is also linoleic acid (Brindza et al., 2009; Tiptiri-Kourpeti et al., 2019). Among the n-3 fatty acids, eicosapentaenoic acid was found between 0% and 0.01 ± 0.01% and docosapentaenoic acid as 0% in 6 genotypes of CM fruits. In addition, total n-3 fatty acids were between 10.87 ± 1.35% fw and 14.71 ± 2.35% fw, and total n-6 fatty acids between 60.19 ± 2.65% fw and 63.47 ± 0.66% fw. Consequentially, n-6/n-3 ratio of CM fruits is between 4.15 and 5.84%, therefore CM consumption may be considered appropriate for a healthy diet (Ersoy et al., 2019).

3.11. Mineral contents

CM fruits and leaves are rich in essential minerals. The concentration of minerals depends on cultivar, growing condition, genotype and

using method. For example, Aslantas, Pirlak, and Guleryuz (2007) used nitric-perchloric acid digest method with atomic emission spectroscopy and found the CM cultivars from Turkey contain (mg/g) potassium (K) 1870; phosphorus (P) 311; calcium (Ca) 570.3; magnesium (Mg) 325; iron (Fe) 0.4; copper (Cu) 6.81; zinc (Zn) 2.59; and manganese (Mn) 7.33, similarly in another study from Turkey using wavelength-dispersive spectrometer method, sodium (Na) 0.16 ± 0.12 mg/g, Mg 2.11 ± 0.12 mg/g, aluminum (Al) 0.95 ± 0.05 mg/g, silicon (Si) 0.40 ± 0.01 mg/g, P 1.06 ± 0.02 mg/g, sulphur (S) 0.40 ± 0.02 mg/g, chlorine (CI) 0.18 ± 0.01 mg/g, K 16.78 ± 0.37 mg/g, Ca 2.43 ± 0.1 mg/g, chrome (Cr) 0.002 ± 0.00 mg/g, Fe 0.035 ± 0.009 mg/g and Zn 0.043 ± 0.007 mg/g are observed in CM fruits (Yigit, Baydas, & Guleryuz, 2009). The 260 genotypes of CM from Serbia contain (mg/g) nickel (Ni) 4.056; P 0.7; K 13.67; Ca 14.6; Mg 0.68; Zn 0.01; Cu 0.003; Fe 0.03; and S 0.98 (Brindza et al., 2009). Gozlekci et al. (2017) study, using an inductively coupled plasma spectrophotometer, found that 20 different genotypes of CM from Turkey contain (mg/g) P 0.32; K 3.07; Ca 0.44; Mg 0.23; Na 0.06; Mn 0.008; Fe 0.03; Cu 0.002 and Zn 0.003 mineral contents are observed. The mean minerals of CM from Turkey, Romania, Italy and Bulgaria (mg/g) P 0.37 ± 0.01; Ca 0.59 ± 0.02; Na 0.08 ± 0.002; Zn 0.003 ± 0.00; Cu 0.001 ± 0.00; and Mn 0.03 ± 0.00 which were found using the mineralize on the absorption spectrometer by Dokoupil and Řezníček (2012). Another study conducted by Ochmian et al. (2019) used the atomic emission spectrometry for K, the flame atomic absorption spectroscopy for Mg Ca, Cu, Zn, Mn and Fe contents and the colorimetric method for P in the leaves and fruits of CM of Shumen cultivars from Poland, which were found to have a higher contents of macro minerals. Compared to rootstock and root mineral quantities, the minerals were not significantly affected by rootstock or root, except Fe and Zn. The mean minerals in the fruits of CM for roots of all cultivars found (mg/g) nitrogen (N) 5.1; P 1.95; K 6.57; Ca 0.85; and Mg 0.55; for rootstocks 5.04; 1.96; 5.38; 1.07; and 0.58, respectively. In the leaves of CM for roots of all cultivars (mg/g) N 30.6; P 2.88; K 21.9; Ca 2.10; and Mg 4.00; for rootstocks 34.4; 2.90; 22.3; 2.22; 4.18, respectively. Karaaslan et al. (2018) determined the mineral analysis of CM fruits using flame atomic absorption spectrometry. They demonstrated the percentage of minerals meeting the diet with Dietary Reference Intake (DRI), which ranged from Ca 32.8 to 42.6%; Fe 15.4 to 34.75%; K 44.5 to 46.4%; Mg 24.8 to 43.3%; and Zn 12.2 to 16.8%. Moreover, Krośniak, Gąstoł, Szałkowski, Zagrodzki, and Derwisz (2010) used the same method and found the highest mineral in CM juice to be K (1639 ± 270 mg/L), followed by Na 324.2 ± 55.8 mg/L, Ca 323.4 ± 93.6 mg/L, Fe 0.483 ± 0.252 mg/L, Zn 0.454 ± 0.037 mg/L, Mn 0.239 ± 0.104 mg/L, and Cu 0.169 ± 0.059 mg/L. CM juice is richer in K, Ca, Na, Fe, Zn, Mn and Cu compared to plum, pear and apple juices, which also has the lowest levels of Cu.

Apart from the spectrometry method, the most commonly used methods are inductively coupled plasma atomic emission spectroscopy (ICP-AES) and quadrupole mass analyzer-single collector (Q-ICP-MS) for mineral analysis. ICP-AES is a method capable of running almost every metal in a large number of samples per day and offer very high throughput. Comparatively, Q-ICP-MS has a good reproducibility and low-cost system but limited resolution and is not well suited for pulsed ionization methods. Studies using ICP-AES, Kalyoncu et al. (2009) analyzed more macro and micro minerals compared to the previous studies, namely mg/g Al 0.005; arsenic (As) 0.0006; boron (B) 0.02; barium (Ba) 0.005; Ca 1.56; Cr 0.0002; Cu 0.002; Fe 0.001; K 14.30; lithium (Li) 0.002; Mg 0.72; Mn 0.001; Na 0.08; Ni 0.0004; P 0.61; S 0.44; selenium (Se) 0.0007; strontium (Sr) 0.01; vanadium (V) 0.003; and Zn 0.002, whereas argent (Ag), bismuth (Bi), cadmium (Cd), cobalt (Co), gallium (Ga) were not found in CM fruits. According to Cindrić, Zeiner, Krpetić, and Stingeder (2012) the fruits and seeds of CM are found to be similar for most of the minerals and contain mg/g: 0.002 and 0.006B, 2.07 and 3.97 Ca, 0.002 and 0.002 Cu, 0.007 and 0.004 Fe, 4.02 and 3.29 K, 0.29 and 0.24 Mg, 0.002 and 0.003 Mn, 0.02 and 0.04Na, 0.009 and 0.007 Ni, 0.003 and 0.003 plumbum (Pb), 0.007 and 0.01 Sr, respectively. In the flesh (mesocarp), total mineral was mg/g: 0.002 Cu, 0.01 Fe, 4.79 K, 0.35 Mg, 0.007Na, 0.01 Ni, 0.003 Pb, and 0.002 Sr. In the fruits and seeds, Cu and Pb were below the limits of detection (0.004 mg/g), whereas in the flesh (mesocarp), Mn, Ca, and Zn were below the limits of detection (2×10^{-9}, 43×10^{-7} and 4×10^{-7} mg/g respectively). Additionally, Cr and Cd are not found in all parts of CM.

Cetkovská et al. (2015) determined the total amount of some minerals of 9 genotypes of CM fruits from Czech Republic using Q-ICP-MS method and found in mg/g quantities: K between 9.73 ± 0.02 and 0.42 ± 0.39; Ca 1.16 ± 0.14 and 0.79 ± 0.05; Mg 0.43 ± 0.04 and 0.07 ± 0.009; Fe 0.002 ± 0.000 and 0.0005 ± 0.0000; Mn 0.002 ± 0.000 and 0.0007 ± 0.0000; Cu 0.004 ± 0.000 and 0.0005 ± 0.0000; Zn 0.004 ± 0.000 and 0.0005 ± 0.0001; Cr 0.0002 ± 0.0000 and 0.00003 ± 0.00000. Lyophilized CM fruits contain lower minerals than fresh CM fruits. These levels were identified in mg/g as follows: K 6.72; Fe 0.006; Cu 0.004; Ca 1.73; and Mg 0.52 (Tiptiri-Kourpeti et al., 2019). The loss may be due to the lyophilization process.

3.12. Vitamin C

Studies showed that the fruits, flowers and leaves of CM contain plenty of vitamin C (ascorbic acid) which vary by the cultivar, genotype and the color of CM in addition to the analytical methods used (Table 3). The vitamin C concentration in CM fruits are found (mg/g fw) between 0.11 and 1.06 (Aslantas et al., 2007; Copur, Soylu, Gurbuz, Degirmencioglu, & Erturk, 2003; Demir & Kalyoncu, 2003; Guleryuz, Bolat, & Pirlak, 1998; Pirlak, Guleryuz, & Bolat, 2003); 0.16 and 0.39 in Ukraine (Brindza, Brindza, Tóth, Klimenko, & Grigorieva, 2007); 0.14 and 1.03 in Greece (Pantelidis et al., 2007); 0.16 and 0.39 in Slovenia (Brindza et al., 2009); 0.36 and 1.03 in Serbia (Jaćimović et al., 2015; Ognjanov et al., 2009); 1.83 and 3.00 in Iran (Hassanpour et al., 2011); 0.34 and 1.89 in Poland (Kostecka, Szot, Czernecki, & Szot, 2017; Kucharska et al., 2011); 0.37 and 0.46 in Italy (De Biaggi et al., 2018); and 0.61 in Czech Republic (Dokoupil & Řezníček, 2012).

To conclude the studies cited in this part, qualitative characteristics and quantitative contents the components of CM depend on multiple factors, such as cultivar, growth and cultivation condition, genotype, maturity fruit color and methods used for content determination. In addition, since the total amount of bioactive components were evaluated using different extracts in the studies, significant differences in values were observed. Extraction is a separation process, hence the difference in solubility is important. Commonly, used solutions are alcohol, ethanol, methanol, etc. Since each substance interacts differently in each solution, it can be interpreted that the solution in which CM dissolves the best will determine the amount of each bioactive component (such as phenolic acids, tannins, anthocyanins, iridoids, etc). This may explain the value differences.

4. Biological properties of *Cornus mas* L.

In vitro studies conducted on the biological effects of the CM to date are shown in Table 4.

4.1. In vitro studies

4.1.1. Antioxidant activity

Antioxidant activity has been identified in polyphenolic compounds as well as ascorbic acid (Bajić-Ljubičić et al., 2018; Dinda et al., 2016; Tural & Koca, 2008). The exact antioxidant capacity of fruits or vegetables can not be determined accurately by a single assay because different components act via different mechanism in *in vitro* and *in vivo* (Dinda et al., 2016). For this reason, many assays have been used for

Table 3
Vitamin C (ascorbic acid) concentration of *Cornus mas* L. according to the used methods.

Vitamin C (ascorbic acid) concentration	Country	Plant part	Method	References
43.78–76.75 mg/100 g fw	Turkey	Fruits	Anonymous (1983)[1]	Guleryuz et al., 1998
35.6–106.3 mg/100 g fw	Turkey	Fruits	Anonymous (1975)[2]	Pirlak et al., 2003
48.39–73.11 mg/100 g fw	Turkey	Fruits	Anonymous (1983)[1]	Demir & Kalyoncu, 2003
10.80–37.36 mg/100 g fw	Turkey	Fruits	Weighted-rankit method	Copur et al., 2003
50.83 mg/100 g fw	Turkey	Fruits	Pelletier and Brassard method[3]	Aslantas et al., 2007
16.4–38.5 mg/100 g fw	Ukraine	Fruits	Unspecified	Brindza et al., 2007
14–103 mg/100 g fw	Greece	Fruits	Reflectometer set of Merck Co (Merck RQflex)	Pantelidis et al., 2007
0.16–0.88 mg/g fw	Turkey	Fruits	Spectrophotometry	Tural & Koca, 2008
28.8 ± 1.9–112.2 ± 4.2 mg/100 g fw	Turkey	Fruits	Reflectometer set of Merck Co (Merck RQflex)	Yilmaz et al., 2009a
16.4–38.5 mg/100 g fw	Slovenia	Fruits	Unspecified	Brindza et al., 2009
73.007 ± 0.090 mg/100 g fw	Turkey	Fruits	Liegel et al.'s method[4]	Kalyoncu et al., 2009
25.00–141.00 mL/100 g fw	Turkey	Fruits	Unspecified	Yalcinkaya, Erbil, & Bas, 2009
29–112 mg/100 mL fw	Turkey	Fruits	Reflectometer set of Merck Co (Merck RQflex)	Yilmaz et al., 2009b
36.1 mg/100 g fw	Serbia	Fruits	Unspecified	Ognjanov et al., 2009
183.25–299.5 mg/100 g fw	Iran	Fruits	Dinitrophenylhydrazine (DNPH) method	Hassanpour et al., 2011
14.96–38.87 mg/100 g fw	Serbia	Fruits	AOAC (1984)[5]	Bijelić et al., 2011
31–70% (the mean value 50%)	Turkey	Fruits	Digital refractometer method	Ercisli et al., 2011
34.29 ± 0.11–75.05 ± 1.32 mg/100 g fw	Poland	Fruits	Not found	Kucharska et al., 2011
1.36 ± 0.17–23.42 ± 0.35 mg/100 g fw	Russia	CM puree	PN-A-04019:1998[6]	Nawirska-Olszańska et al., 2011
61 mg/100 g fw	Czech Republic	Fruits	Modified method according to Miki[7]	Dokoupil & Řezníček, 2012
240–360 mg /100 g fw	Iran	Fruits	DNPH method	Hassanpour et al., 2012
52–103 mg/100 g fw	Serbia	Fruits	AOAC (1984)[5]	Jaćimović et al., 2015
188.92 ± 0.14 mg/100 g fw	Poland	Fruits	Titration method	Kostecka et al., 2017
196.31 ± 0.23 mg/100 g fw			Iodometric metod	
67.47 ± 0.14 mg/100 g fw			Spectrophotometric metod	
73.97 ± 0.14 mg/100 g fw			Fluorimetric metod	
63.1 ± 0.11 mg/100 g fw			HPLC method	
55.10 ± 0.13 mg/100 g fw			Enzymatic method	
41.98 ± 4.56 mg/100 g fw	Italy	Fruits	HPLC	De Biaggi et al., 2018
54.9–75.97 mg/100 g fw	Poland	Fruits	Titration method	Szot et al., 2019
For ownroot; 41.7 mg/kg; for rootstock; 45.3 mg/100 g fw	Poland	Fruits	Reflectometer set of Merck Co (Merck RQflex)	Ochmian et al., 2019

fw, fresh weight; mg, milligram; g, gram; HPLC, high performance liquid chromatography; [1] Gıda Maddeleri Muayene ve Analiz Yontemleri, Republic of Turkey, General Directorate of Agricultural Forestry and Rural Affairs, Publication no: 65, Special Publication no:2–105, Ankara; [2]Official Methods of Analysis. Association of Official Analitical Chemists, Washington, D.C.;[3]O. Pelletier, R. Brassard. Determination of vitamin C (L-ascorbic acid and dehydroascorbic acid) in food by manual and automated photometric methods. Journal of Food Science. 42(6) (1977) 1471–1477; [4] Liegel, 1974. Prakticum Zum Obstbau, Lehrstuhl Für Obstbau und Gemusebeau, Der Universitat Hohenheim, 31–38;[5] Officials methods of analysis. 14th ed. AOAC, VA.;[6]Produkty spożywcze – Oznaczanie zawartości witaminy C [Foodstuffs – Determination of ascorbic acid content]. [in Polish];[7]N. Miki, High-performance liquid-chromatographic determination of ascorbic acid in tomato products. Journal of the Japanese Society for Food Science and Technology-Nippon Shokuhin Kagaku Kogaku Kaishi, 28 (5) (1981) 264–268.

evaluating the antioxidant activity Perova of the different parts of CM. The 1,1-diphenyl-2-picryl-hydrazyl method (DPPH) radical inhibition test is one of the most widely used, (Antolak et al., 2017; Celep et al., 2012; Cetkovská et al., 2015; Cosmulescu et al., 2019; Dragović-Uzelac et al., 2007; Gulcin, Beydemir, Sat, & Kufrevioglu, 2005; Hassanpour et al., 2011; Kucharska et al., 2011; Milenković-Andjelković et al., 2015; Okan et al., 2019; Šamec & Piljac-Žegarac, 2015; Stankovic et al., 2014; Tural & Koca, 2008), followed by the ferric-reducing antioxidant properties method (FRAP) (Capanoglu et al., 2011; De Biaggi et al., 2018; Dragović-Uzelac et al., 2007; Gulcin et al., 2005; Kucharska et al., 2011; Moldovan et al., 2016b; Ochmian et al., 2019; Okan et al., 2019; Pantelidis et al., 2007; Petridis, Koukourikou, Sotiropoulos, & Stylianidis, 2010; Tural & Koca, 2008) and 2,2-azinobis (3-ethylbenzothiazoline-6-sulfonic acid) radical cation (ABTS) (Capanoglu et al., 2011; Dragović-Uzelac et al., 2007; Kucharska et al., 2011; Ochmian et al., 2019; Šamec & Piljac-Žegarac, 2015). The others are oxygen radical absorbance capacity (ORAC) (Dragović-Uzelac et al., 2007), oxygen anti-radical power (O_2-ARP) (Gulcin et al., 2005; Pantelidis et al., 2007), hydrogen peroxide (H_2O_2) inhibition effect (Gulcin et al., 2005), total antioxidant capacity (TOAC) (Celep et al., 2012), copper reducing antioxidant capacity (CURRAP) (Celep et al., 2012), β-carotene bleaching (Celep et al., 2012; Sengul et al., 2014), antioxidant capacity of the liposoluble (ACI) (Andronie et al., 2019), metal chelating assays (Gulcin et al., 2005) and superoxide-ARP (Celep et al., 2012). CM fruits showed the strongest radical scavenging activity compared to sour cherry (*Prunus cerasus*) and laurel cherry (*Prunus laura cerasus*) (Capanoglu et al., 2011). In contrast CM fruits exhibited the lowest antioxidant activity according to the DPPH assay compared to elderberry and lingonberry fruits, whereas the highest activity is found in the FRAP assay (Antolak et al., 2017). Moreover, the antioxidant activity of ethanol (Karaaslan et al., 2018; Popović et al., 2012; Stankovic et al., 2014; Szczepaniak et al., 2019b), methanol (Celep et al., 2013; Ersoy, Bagci, & Gok, 2011; Karaaslan et al., 2018; Stankovic et al., 2014; Tarko et al., 2017b; Yilmaz et al., 2009a), ethyl acetate (Stankovic et al., 2014), acetone (Karaaslan et al., 2018), petroleum ether (Stankovic et al., 2014) acetonitrile (Karaaslan et al., 2018), or water extracts (Gulcin et al., 2005; Popović et al., 2012; Szczepaniak et al., 2019b) of various genotypes of CM have been evaluated by several groups in *in vitro* studies. These studies showed that methanol, ethanol and acetone extracts of CM exhibited strong antioxidant activity compared to water and petroleum ether extracts (Karaaslan et al., 2018; Stankovic et al., 2014). In contrast, Szczepaniak et al. (2019a) found the antioxidant power of water extract of CM fruits shows the highest value in the ABTS assay, whereas ethanol extract of CM fruits shows the highest value in the DPPH assay. Acetone extract of CM flowers and leaves showed the highest results for antioxidant activity, while ethyl acetate extract of CM fruits showed to the highest (Stankovic et al., 2014). The antioxidant power of 50% water methanol extract of CM fruits were higher in the DPPH assay with 0.716 ± 0.07 $1/EC_{50}$ (efficient concentration) anti-radical activity and Fe^{2+} chelating assay with 54.24%; values in CM leaves were 0.928 ± 0.13 $1/EC_{50}$ and 28.43 ± 2.79% compared to the other *Cornus* species, respectively (Serteser et al., 2009).

The antioxidant capacity of CM juice (Gąstoł et al., 2013), CM liqueur (Sokoł-Łętowska et al., 2014; Tarko et al., 2014), CM wine (Tarko et al., 2014), in addition adding CM juice in different fruits juices

Table 4
Summary of biological activities of *Cornus Mas* L. for *in vitro* studies.

Activity tested	Model	Extract/compound or part of CM	Effect	References
Antioxidant	FRAP, DPPH, O_2 antiradical power, H_2O_2 inhibition effect, metal chelating assays	Water extr. of CM fruits from Serbia	Showed significant antioxidant activity in all these assays. The effect at 60 μg/mL of CM fruits on the inhibition of peroxidation of linoleic acid emulsion was 97.5% and comparable to that of standard antioxidant 96.5% in BHA and 99.2% in BHT.	Gulcin et al., 2005
	ABTS, DPPH, FRAP, ORAC assays	Two cultivars of CM fruits from Zagreb	Antioxidant power was found 18.04 ± 1.95 to 25.09 ± 2.05 mmol Fe^{+2}/kg in FRAP assay; 33.41 ± 2.15 to 39.89 ± 3.05 mmol Trolox / kg in DPPH assay; 29.48 ± 3.05 to 36.51 ± 2.05 mmol Trolox/kg in ABTS assay; and 119.16 ± 7.15 to 175.91 ± 8.22 mmol Trolox / kg in ORAC assay.	Dragović-Uzelac et al., 2007
	FRAP, –OH radical scavenging	CM fruits of Vermio	Antioxidant activity was found 83.9 ± 5.4 μmol AA/kg in FRAP assay; and 98.6 ± 0.3% deoxyribose protection in –OH radical scavenging.	Pantelidis et al., 2007
	FRAP and DPPH assays	Twenty four cultivars of CM fruits from Turkey	Fruits of cultivars showed highest antioxidant activity, which depending on the method used was FRAP unit 16.21–94.43 mmol/g (FRAP) and EC_{50} value of 0.29–0.69 mg/mL (DPPH).	Tural & Koca, 2008
	TOAC	Tarhana with CM	The mean TOAC value were found 7.03 ± 2.11 mmol.	Koca, 2008
	β-carotene bleaching and FRAP assays	Methanol extr. of 16 genotypes CM fruits from Turkey	Showed highest antioxidant capacity using both methods. 13–90.13% for β-carotene bleaching; and 73 to 114 μmol AsA/g for FRAP assay.	Yilmaz et al., 2009a
	H_2O_2 scavenging, Fe^{2+} chelating assay, DPPH assays	50% water methanol extr. of 38 wild plants from Turkey	Antioxidant power of 50% water methanol extr. of CM fruits were higher in DPPH assay with 0.716 ± 0.07 $1/EC_{50}$ anti-radical activity and Fe^{2+} chelating assay with 54.24%; also these values in CM leaves were 0.928 ± 0.13 $1/EC_{50}$ and 28.43 ± 2.79%, respectively.	Serteser et al., 2009
	FRAP assay	CM fruits from Greece	FRAP value was 80.15 ± 19.78 μmol AAE/g.	Petridis et al., 2010
	β-carotene bleaching assay	CM pestil	β-carotene bleaching value was 70.59 ± 1.9%.	Sengul, Yildiz, Gungor, & Okcu, 2010
	DPPH assay	CM puree	CM puree's antioxidant activity was found 27 μM Trolox/g (DPPH).	Nawirska-Olszańska et al., 2011
	ABTS, FRAP, CURRAP assays	CM fruits from Turkey	Showed stronge radical scavenging activity with ABTS 50.8 ± 2.0 mmol TEAC/100 g; CURRAP 76.3 ± 3.6 mmol TEAC/100 g; FRAP 22.3 ± 0.9 mmol TEAC/100 g.	Capanoglu et al., 2011
	DPPH, FRAP, ABTS assays	Ten cultivars of CM fruits from Poland	Especialy fruits of Szafer varieties showed higher antioxidant activity with 19.0 μM Trolox/g (DPPH), 39.0 μM Trolox/g (ABTS) 41.1 μM Trolox/g (FRAP).	Kucharska et al., 2011
	FRAP assay	CM juice, UF permeate, MOD retentate CM juice	There was no statistically significant difference antioxidant activity between fresh juice and MOD retentate used juice. According to the FRAP assay, it was found for fresh juice 12.77 ± 1.23 mg AA/L, UF permeate 12.33 ± 1.82 mg AA/L, and MOD retentate 11.35 ± 1.41 mg AA/L.	Bélafi-Bakó & Boór, 2011
	DPPH assay	Six CM fruits genotypes from East Azerbaijan	Antioxidant power were found 38.98–82.37% in DPPH assay.	Hassanpour et al., 2011
	DPPH, Fe^{+2} chelating assay, H_2O_2 inhibition effect assays	50% water methanol extract of twelve CM fruits genotypes from Turkey	Antioxidant activity of EC_{50} value of 1.060 to 1.863 (DPPH), 33.883 to 54.213% (Fe^{2+} chelating activity) and 37.720 to 79.103% (H_2O_2 inhibition).	Ersoy et al., 2011
	DPPH, Fe^{+2} chelating assay, ORAC assays	CM puree	Antioxidant activity was found 73.30 ± 4.07% in DPPH; 43.20 ± 2.83 mmol Fe^{+2}/mL in Fe^{+2} reducing power; and 41.94 ± 15.99 μmol TE/mL in ORAC for CM puree.	West et al., 2012a
		CM fruits from Turkey		Celep et al., 2012

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Table 4 (*continued*)

Activity tested	Model	Extract/compound or part of CM	Effect	References
	DPPH and superoxide radical-scavenging activity, FRAP,CURRAP, metal-chelating assay, TOAC, β-carotene bleaching, TEAC assays		Antioxidant activity was found EC_{50} value of 735 ± 17.5 (DPPH), 11.61 ± 0.48 (superoxide radical scavenging activity), 0.42 ± 0.01 (FRAP), 20.9 ± 0.10 (CURRAP), 65 ± 1.6 (β-carotene bleaching), 66.06 ± 3.19 (TOAC), and 103 ± 8.9 (TEAC).	
	FRAP, PRAC, DPPH, NO-ARP, O_2-ARP, OH-ARP assays	80% ethanol extr. of ten genotypes of CM fruits from Serbia	Anti radical power of CM fruits was found $1/IC_{50}$x100 value of 0.394–1.322 in DPPH; 0.112–0.231 in NO-ARP; 0.494–1.31 in O_2-ARP; 5.47–8.58 in OH-ARP; and antioxidant activity was found 0.726–1.15 A_{50} for PRAC assay and 21–57.8 FRAP unit for FRAP assay.	Popović et al., 2012
	FRAP assay	CM juice	FRAP value was found 23.5 mmol Fe/L.	Gąstoł et al., 2013
	ABTS assay	Light yellow, blush, light red, dark red CM fruits from Turkey	The overall average for the ABTS was found 36.3 μmol TE/g and the values were reduced at the dark red fruits. It was found 55.0 μmol TE/g in light yellow fruits; 55.3 μmol TE/g in blush fruits; 27.1 μmol TE/g in light red fruits; and 7.8 μmol TE/g dark red fruits.	Gunduz et al., 2013
	DPPH, Superoxide, FRAP, CUPRAC, β-carotene, TOAC, TEAC assays	80% methanol extr. of CM leaves from Turkey	Showed strong antioxidant activity in all the tested assays. In DPPH assay, it exhibited E_{C50} value of 165 μg/mL, which was comparable to that of BHT (133 μg/mL). In β-carotene assay, it showed 93% activity, comparable to that of BHT (96%).	Celep et al., 2013
	DPPH assay	Methanol, water, ethyl acetate, acetone, petroleum ether extr. of CM fruits, leaves and flowers from Serbia	Antioxidant activity of fruit extracts is expressed as IC_{50} values (mg/mL) that range from 518.47 (in ethyl acetate extr.) to 11.06 (in acetone extr.) μg/mL; IC values of leaves were found 32.17 ± 0.44 (in acetone extr.) to 81.34 ± 1.32 (in ethyl acetate extr.) and for flowers the range from 27.58 ± 0.64 (in methanol extr.) to 470.27 ± 1.21(in ethyl acetate extr.). Acetone extr. as well as methanol and water extr. from leaves showed very strong activity.	Stankovic et al., 2014
	β-carotene bleaching assay	Five genotypes of CM fruits from Turkey	β-carotene bleaching value ranged 85.07 and 97.96%	Sengul et al., 2014
	DPPH assay	CM liqueur	DPPH value was 329 μnol TE.	Sokoł-Łętowska et al., 2014
	ABTS assay	Fruits, liqueur and wine of CM fruits	ABTS was found (μmol Trolox/g) 7123.0 ± 14.62 in fresh CM fruits; 731.2 ± 26.99 in CM wine; and 5064.2 ± 248.94 in CM liqueur.	Tarko et al., 2014
	ABTS assay	Apple, orange and grapefruit juice with CM	ABTS values were 207 ± 1.3 mg trolox/100 mL in beverage with apple and 2% CM fruits, and 323 ± 2.3 in beverage grapefruit and 2% CM fruits, and 396 ± 3.3 in grapefruit and 10% CM fruits.	Tarko et al., 2015
	DPPH, ABTS assays	Fresh and stored at −20° C for 12 months of CM fruits	According to the DPPH method, it was found 3.5 ± 0.1 mmol TEAC/100 g in fresh CM fruits; 3.1 ± 0.1 mmol TEAC/100 g in CM which stored at −20° C for 12 months; According to the ABTS method, these values were found 5.5 ± 0.1 and 5.5 ± 0.0 mmol TEAC/100 g, respectively.	Šamec & Piljac-Žegarac, 2015
	DPPH assay	Nine cultivars CM fruits from Czech Republic	DPPH value ranged 29.55 ± 1.75 and 67.25%.	Cetkovská et al., 2015
	DPPH assay	CM fruits and leaves from Serbia	Both fruits and leaves showed strong radical scavenging activity with EC_{50} values of 0.94 and 0.47 mg/mL, respectively.	Milenković-Andjelković et al., 2015
	FRAP, ABTS assays	CM fruits from Romania	Showed strong radical scavenging activity with μmol TE/100 g value of 677.88 ± 19.25 (ABTS) and 628.75 ± 17.41 (FRAP).	Moldovan et al., 2016a

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Table 4 (*continued*)

Activity tested	Model	Extract/compound or part of CM	Effect	References
	ABTS, FRAP, HPTLC assays	Acetone extr. of CM fruits stored at 22 °C for 19 days	No major differences in the total antioxidant capacity and activity during storage period. The antioxidant capacity for 0 day ranged 12.9 and 19 day 12.83 μmol Trolox/g fruit (HPTLC assay); 36.13 to 33.93 μmol Trolox/g fruit (ABTS assay) and 33.51 ± 1.27 to 32.43 ± 1.12 μmol Trolox/g fruit (FRAP assay).	Hosu et al., 2016
	ABTS, FRAP assays	Acetone extr. of CM fruits stored at 2 °C or 75 °C	CM fruits stored at 2 °C after 60 days showed a 10% decreased in ABTS values and a 17% decreased in FRAP values. CM fruits stored at 75 °C showed a 29% reduction in both methods.	Moldovan et al., 2017
	DPPH, FRAP assays	CM fruits from Poland	It was found IC_{50} value of 0.045 ± 0.001 (DPPH) and 0.042 ± 0.001 (FRAP).	Antolak et al., 2017
	ABTS assay	80% methanol, 80% ethanol, water and methyl chloride extr. of CM fruits	Antioxidant activities according to ABTS assay; 15.77 ± 0.33 in 80% methanol, 9.76 ± 0.15 in 80% ethanol, 3.43 ± 0.15 in water and 0.01 ± 0.00 g/kg in methyl chloride extr.of CM fruits were found.	Tarko et al., 2017b
	ABTS assay	Apple chips with CM fruits	ABTS assay value was found 1631 ± 26 mg trolox/100 g.	Tarko, Duda-Chodak, & Semik-Szczurak, 2017a
	DPPH, ABTS assays	Acetone, acetonitrile, ethanol, methanol and water extr. of CM fruits	Acetone extr. of CM demonstrated the highest results, whereas the lowest results were obtained from water extr. for both assays. Antioxidant activities in acetone, acetonitrile, ethanol, methanol and water extr. for CM were found 1053.72 ± 38.12, 724.49 ± 29.18, 922.66 ± 21.64, 933.48 ± 22.61 and 508.12 ± 5.11 mg TEAC/100 g in DPPH and 2907.34 ± 152.05, 808.35 ± 11.16, 1567.68 ± 53.27, 1735.63 ± 91.30 and 506.08 ± 10.36 mg TEAC/100 g in ABTS, respectively.	Karaaslan et al., 2018
	DPPH, FRAP assays	Fresh, dried and compote of CM fruits	Fresh CM fruits showed the highest antioxidant activity with 29.91 ± 0.76 to 97.21 ± 0.76 mmol TE/g (DPPH assay) and 29.12 ± 0.26 to 94.64 ± 0.26 mmol TE/g (FRAP assay). These values were found for dried CM fruits 46.58 ± 3.34 and 48.53 ± 0.32 mmolTE/g; compote CM fruits 46.58 ± 3.34 and 14.63 to 80.32 ± 5.04 and 13.12 ± 014 to 72.03 ± 0.14 mmol TE/g, respectively.	Petkova & Ognyanov, 2018
	FRAP assay	Chieri genotype of CM fruits	It was found 20.41 ± 0.50 mmol Fe^{+2}/kg (FRAP).	De Biaggi et al., 2018
	DPPH assay	CM fruits from Romania	Antioxidant capacity was found 1.91 ± 0.25 mmol trolox/100 g (DPPH).	Cosmulescu et al., 2019
	DPPH, ABTS assays	Water and 40% ethanol extr. of seven genotypes of CM fruits from Poland	The mean inhibition rate for all genotypes was found 36.759 ± 26.793% (ABTS) and for all genotypes ABTS (mmol TE/100 g dw) ranged from 0.392 ± 0.023 and 6.591 ± 0.090, DPPH (mmol TE/100 g dw) ranged from 0.8546 ± 0.1849 and 10.3980 ± 0.4282. In addition, the highest ABTS radical scavenging activity and inhibition rate were found for the water extr. of Słowianin and Szafer cultivars and ethanol extr. of cultivars Jolico and Wydubiecki.	Szczepaniak et al., 2019b
	DPPH assay	Lyophilized CM juice	Showed strong antioxidant activity with IC_{50} value of 0.067 ± 0.001% (DPPH).	Tiptiri-Kourpeti et al., 2019
	DPPH, ABTS, FRAP assays	Fermented apple-CM beverages (added yellow, coral or red CM fruits)	The strongest antioxidant activity was showed in the beverage with the addition of red CM fruits with 7.90 mmol TE/L (DPPH), 11.04 mmol TE/L (ABTS), and 12.86 mmol TE/L (FRAP).	Adamenko et al., 2019

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Table 4 (*continued*)

Activity tested	Model	Extract/compound or part of CM	Effect	References
	DPPH, Fe^{+2} chelating assay, NO radical scavenging assays	Frozen at −20 °C, %70 ethanol extr. of CM fruits	Ethanol extr. of CM fruits showed the most effective antioxidant activity in the FRAP assay with 81.37–90.66% and anti-tyrosinase inhibition capacity with 21.75–74.23% but was not able to scavenge NO.	Natić et al., 2019
	DPPH, ABTS, FRAP assays	CM beer (added yellow, coral or red CM fruits)	The highest antioxidant activity was found beer with the addition of red CM fruit juice produced with the M−2 method. The lowest antioxidant activity was found beer with the addition of coral CM fruit compared to the others. It was found with mmol TE/L of value 6.41 ± 0.1 (DPPH) 6.51 ± 0.81 (ABTS) and 2.6 ± 0.02 (FRAP) in the beer with red CM juice; in the beer with coral CM juice 5.59 ± 0.1, 4.77 ± 0.06 and 1.95 ± 0.07, respectively (M−2 production method in which 10% of post-fermentation liquid was replaced by CM juice).	Kawa-Rygielska et al., 2019
	DPPH, FRAP assays	CM fruits from Turkey	Showed strong antioxidant activity with 0.22 ± 0.01 mg/mL (DPPH) and 168.02 ± 7.41 μM $FeSO_4{\cdot}7H_2O$/g (FRAP).	Okan et al., 2019
	ABTS, DPPH assays	CM fruits from Poland	CM fruits 'Jolico' from rootstock were characterized by the highest radical scavenging activity (DPPH 40.9 μmol g/L, ABTS 48.7 μmol g/L).	Ochmian et al., 2019
	ACI assay	CM fruits from Romania	ACI value was found 25.15 1.65 μg/mg AAE.	Andronie et al., 2019
	DPPH assay	Air dried CM fruits	DPPH value was RC_{50} value of 246.2 ± 0.2.	Abbasi et al., 2020
Anti-microbial	Disc diffusion method	Methanol and water extr. of CM fruits and CM juice	Significant activity against *Bacillus subtilis, Bacillus cereus, Escherichia coli and Serratia marcescens*	Krisch et al., 2008
	Disc diffusion method	Methanol and ethanol extr. of CM fruits, seeds, leaves and barks	Methanol extr. of CM fruits had a moderate effect on *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa*; and ethanol extr. of CM fruits had a moderate effect on *Escherichia coli* and *Pseudomonas aeruginosa*. Methanol extr. of CM seeds showed strong effect on *Staphylococcus aureus, fungi Candida* and *Aspergillus fumigates*, whereas ethanol extr. of CM seeds effect on *Staphylococcus aureus* and *Candida albicans*. Ethanol extr. of CM leavest had strong effect on *Staphylococcus aureus* and *Candida albicans*; and ethanol extr. of CM barks had a poor effect on *Staphylococcus aureus* and *Pseudomonas aeruginosa.*	Krzyściak et al., 2011
	Disc diffusion method	Methanol/acetone/water/ formic acid (30/42/27.5/0.5) extr. of CM fruits and leaves	Both extracts of fruits and leaves showed moderate activity against 13 bacterial and fungal strains, *Clostridium perfringens, Bacillus cereus, Staphylococcus aureus, Listeria monocytogenes, Sarcina lutea, Micrococcus flavus, Escherichia coli, Pseudomonas aeruginosa, Salmonella enteritidis, Shigella sonnei, Klebsiella pneumonia, Proteus vulgaris and Candida albicans.*	Milenković-Andjelković et al., 2015
	Disc diffusion method	PBS, PBS and water, water and methanol extr. of CM fruits	All extracts of CM showed potent activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* after 7 days and no bacterial growth was observed until 28th day.	Kyriakopoulos & Dinda, 2015
Anti-microbial and cytotoxic	Potato disc method Disc diffusion method	Water and ethanol extr. of CM fruits	Hot ethanol extr. of CM fruits (50° C) showed significant antibacterial activity against *Staphylococcus aureus, Staphylococcus epidermidis* and *Streptococcus pyogenes*. According to potato disc method, CM did not exhibit cytotoxic activity.	Turker et al., 2012

(*continued on next page*)

Table 4 (*continued*)

Activity tested	Model	Extract/compound or part of CM	Effect	References
Cytotoxic	MTT assay	Methanol extr. of air-dried CM leaves and flowers	The methanol extract of flowers and leaves of air-dried CM exibited significantly cytotoxic effect against HeLa and human colon carcinoma LS174 cells lines.	Šavikin et al., 2009
	MTT assay	80% ethanol extr. of CM fruits	In all cancer cells, the CM extract reduced cell viability to below 26%, even at the lowest doses. Average growth inhibition was 81.8%, 81.9%, 81.6% and 79.3% in SKOV3, MCF-7, PC-3 and A549 cells, respectively.	Yousefi et al., 2015
	Colorimetric assay	Water extr. of CM fruits	750 μg/mL of water extract of CM fruits inhibited MCF-7 cells.	Forman et al., 2015
	Sulforhodamine B assay	CM juice	CM juice showed the highest antitumor activity against human HepG2 cells followed by murine CT26 cells. Human Caco2 and HT-29 exhibited similar sensitivity, which is weaker than its murine counterparts and about four to six times weaker than human HepG2 cells. Also, MCF-7 exhibited the highest resistance.	Tiptiri-Kourpeti et al., 2019
	Cell Titer Blue assay	AuNPs-CM	The cytotoxic effect was significant at doses higher than 20 μg/mL. The cytotoxic effect was higher in HaCaT cells compared to the other cell line, in accordance with the higher uptake in these cells after 24 h incubation. The concentrations which reduced the cell population by 50% (IC_{50}) were 23.9 μg/mL for HaCaT cells and 28.19 μg/mL for A431 cells.	Perde-Schrepler et al., 2016
	Colorimetric assay	AuNPs, AgNPs and water extr. of CM fruits	AuNPs stimulated the proliferation of HGF cell lines, a dose-dependent effect up to 50 μg/mL, then viability was decreased. DOK cells viability was decreased by AuNPs, AgNPs and CM extract in a dose dependent manner. CM extract showed only a low decrease, at high doses (≥50 μg/mL). AuNPs showed the highest toxicity against DOK cells, since viability was already decreased compared with controls at 10 μg/mL.	Baldea et al., 2020
Renal protective	MTT assay	Deionized water extr. of CM fruits	In the cisplatin group combined with deionized water exr. of CM fruits were significantly reduced the harmful effects of cisplatin in African green monkey kidney epithelial cells (Vero). MDA levels decreased and GSH, GPx and SOD increased in CM + cisplatin group.	Yarim et al., 2017
Hypolipidemic	Flouresan assay	Water and ethanol extr. of fresh and lyophilized CM	Water and ethanol extracts of fresh and lyophilized CM showed an inhibitory effect on LP, but only significant difference was found in a water extract of fresh CM fruits (134 ± 6.4 mg/mL) on α-amylase inhibition.	Świerczewska et al., 2019

O_2, oxygen; H_2O_2, hydrogen peroxide; Fe^{+2}, iron (II); OH, hydroxide; $FeSO_4$, iron II sulphate; μg; microgram; mL, mililiter; mmol, millimole; g, gram; kg, kilogram; mg, milligram; mL, milliliter; μmol, micromole; extr, extract; dw, dry weight; FRAP, ferric-reducing antioxidant power; DPPH, 1,1-diphenyl-2-picryl-hydrazyl; BHA, butylated hydroxyanisole; BHT, butylated hydroxytoluene; ABTS, 2,2-azinobis(3-ethylbenzothiazolyne-6-sulphonic acid) radical cation; ORAC; oxygen radical absorbance capacity; PRAC, permanganate reducing antioxidant capacity; TOAC, total antioxidant capacity; NO-ARP, nitric oxide anti radical power; O2-ARP, oxygen anti radical power; OH-ARP, hydroxide anti radical power; CURRAP, copper reducing antioxidant capacity; ACI, antioxidant capacity of the liposoluble; HPTLC, high-performance thin-layer chromatography; TEAC, trolox equivalent antioxidant capacity; TE, trolox equivalents; EC_{50}, μg/mL; IC_{50}, The concentration (in the final reaction medium in each method) that causes a decrease in the initial absorbance (control) by 50%; A_{50}, mmol ascorbate equivalents/g; AA, ascorbic acid; AAE, L-ascorbic acid equivalents; PBS, phosphate buffer saline; MDA, malondialdehyde; GSH, glutathione reductase; GPx, glutathione peroxidase; SOD, superoxide dismutase; LP, lipoprotein lipase; MOD, membrane osmotic distillation; AuNPs-CM, gold nanoparticles with water extr. of CM fruits; AuNPs, gold nanoparticles, AgNPs, silver nanoparticles; HeLA, cervix adenocarcinoma cells; SKOV3, ovarian cancer cells; MCF-7, breast adenocarcinoma cells; PC-3, prostate adenocarcinoma cells; A549, lung non small cell cancer; HepG2, human liver carcinoma cells; CT26, murine colorectal carcinoma cells; HT-29, human colon cancer cells; Caco2, human colon cancer cells; HaCaT, human keratinocyte cell lines; A431, epidermoid carcinoma cell lines; HGF, human gingival fibroblasts; DOK, Human Caucasian dysplastic oral keratinocytes.

(Adamenko, Kawa-Rygielska, Kucharska, & Piórecki, 2019; Tarko, Duda-Chodak, Semik, & Nycz, 2015) and adding CM fruits in beer (Kawa-Rygielska et al., 2019) have been determined in the literature on the subject (Table 4). CM juice showed about 10-fold higher antioxidant capacity than plum, pear and apple juices (Gąstoł et al., 2013). As a result of adding CM juice in apple juices, antioxidant capacity increased 2–3 fold compared to puree apple juice. In particular, this increase had reached the highest rates with the addition of red CM juice (Adamenko et al., 2019). Moreover, no significant decrease in antioxidant capacity was found between the pure of CM juice and membrane osmotic distillation (MOD) retentate CM juice (Bélafi-Bakó & Boór, 2011).

The values of the antioxidant capacity of stored CM fruits depend on temperature. Moldovan, David, and Man (2017) showed a 10% decrease in the antioxidant capacity of CM fruits stored at 2 °C for 60 days. However, higher losses were observed with storage at 75 °C and decreased by an average of 29% after 10 days because of capacity a reduction in the total amount of vitamin C. Similarly, Hosu et al. (2016) found no significant differences between fresh and stored CM fruits at 22 °C for 19 days. Air-dried methods, cause a decrease in the high levels of bioactive components. For example, air-dried CM fruits showed lower antioxidant activity with 246.2 ± 0.2 RC_{50} (50% reduction capacity) in DPPH assay (Abbasi et al., 2020). Whereas lyophilized methods lead to minimal loss of bioactive components, which were proved by the studies (Natić et al., 2019; Šamec & Piljac-Žegarac, 2015; Tiptiri-Kourpeti et al., 2019). In addition, CM leaves have found lower antioxidant activity than CM fruits (Table 4). Most of the antioxidant activity assays of CM fruits suggested that its rich source of natural antioxidant components can be used as a functional food. Also, the reasons why antioxidant activity values differ in studies, as in bioactive components, are due to the usage of the different solutions and assays.

4.1.2. Anti-microbial activity

Due to the lower incidence of side effects (Dinda et al., 2016), medicinal plants have been very popular, especially in the treatment of diseases, particularly infectious diseases in recent years (Aslantas et al., 2007; Yigit et al., 2009). Amongst the literature, the anti-microbial activity of extracts of CM fruits and leaves is generally evaluated by the disc diffusion method (Krisch, Galgóczy, Tölgyesì, Papp, & Vágvölgyi, 2008; Krzyściak, Krośniak, Gąstoł, Ochońska, & Krzyściak, 2011; Kyriakopoulos & Dinda, 2015; Milenković-Andjelković et al., 2015). For example, 50 °C hot ethanol extract of CM fruits showed strong antibacterial activity against *Staphylococcus aureus, Staphylococcus epidermidis* and *Streptococcus pyogenes* (Turker, Yildirim, & Karakas, 2012). Also, phosphate buffer saline (PBS) and water extracts of CM fruits (20 mL) inhibited *Staphylococcus aureus* and *Pseudomonas aeruginosa* after 7 days and no bacterial growth observed until the 28th day (Kyriakopoulos & Dinda, 2015). Milenković-Andjelković et al. (2015) found significant anti-microbial activity of methanol/acetone/water/formic acid (30/42/27.5/0.5) extract of CM fruits and leaves (30 μg/disc) against *Clostridium perfringens, Bacillus cereus, Staphylococcus aureus, Listeria monocytogenes, Sarcina lutea, Mariniluteicoccus flavus, Escherichia coli, Pseudomonas aeruginosa, Salmonella enteritidis, Shigella sonnei, Klebsiella pneumoniae, Proteus vulgaris* and *Candida albicans*. With the exception of the anti-microbial activity of fruits, methanol and ethanol extracts of CM seeds, leaves and barks (200 μg/disc 24 h for bacteria and 48 h for fungus) showed strong anti-microbial activity. Methanol extract of CM seeds inhibited *Staphylococcus aureus,* fungi Candida and *Aspergillus fumigatus*, whereas ethanol extract of CM seeds inhibited *Staphylococcus aureus* and *Candida albicans*. Ethanol extract of CM leaves had significant antimicrobial activity against *Staphylococcus aureus* and *Candida albicans*. Ethanol extract of CM barks had a poor effect on *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Methanol extract of CM fruits showed moderate effect on *Staphylococcus aureus, Escherichia coli* and *Pseudomonas aeruginosa* whereas ethanol extract of CM fruits showed a moderate effect on *Escherichia coli* and *Pseudomonas aeruginosa* (Krzyściak et al., 2011). Administration dose of 100 μL/disc of CM juice, methanol and water extracts of CM fruits showed significant anti-microbial activity against *Bacillus subtilis, Bacillus cereus, Escherichia coli* and *Serratia marcescens* (Krisch et al., 2008). Studies have mostly evaluated the methanol, water and ethanol extracts of CM as anti-microbial activity; and according to the studies, it can be said that methanol and ethanol extracts of all part of CM have strong anti-microbial activity.

4.1.3. Cytotoxic activity

According to the potato disc method, CM fruits are found to have less cytotoxic activity than guelder rose (*Viburnum opulus* L.), wayfaring tree (*Viburnum lantana* L.), firethorn *(Pyracantha coccinea Roemer),* dewberry *(Rubus caesius* L.), *Crataegus tanacetifolia (Lam.) Pers (tansy-leaved thorn),* hawthorn (*Crataegus monogyna Jacq.)* and dog rose *(Rosa canina* L.) (Turker et al., 2012). Yousefi, Abasi, Abbasi, and Jahanban-Esfahlan (2015) investigated the cytotoxicity of different doses of 80% ethanol extract of CM fruits (0, 5, 20, 100, 250, 500, 1000 μg/mL) towards A549 (lung non small cell cancer), MCF-7 (breast adenocarcinoma), SKOV3 (ovarian cancer) and PC-3 (prostate adenocarcinoma) cells and showed that all doses showed cytotoxic activity against ovarian, breast, prostate and lung cancer cells, in addition to reducing cancer cell viability below 26% at even the lowest doses (5 μg/mL). Moreover, methanol extract of CM flowers and leaves (200 μg/ml) exhibited a significant cytotoxic effect against cervix adenocarcinoma HeLa and human colon carcinoma LS174 cell lines after 72 h treatment (Šavikin et al., 2009). The water extract of CM leaves inhibited MCF-7 cell lines at the dose of 750 μg/mL (Forman, Haladová, Grančai, & Ficková, 2015). In addition, concentrations of 0.007–1% of CM juice for 72 h showed the highest cytotoxic activity against human liver carcinoma HepG2 cells followed by murine colorectal carcinoma CT26 cells. Human colon cancer cells (Caco2 and HT-29) exhibited similar sensitivity, which is weaker than its murine counterparts and about four to six times weaker than human HepG2 cells. Also, MCF-7 exhibited the highest resistance (Tiptiri-Kourpeti et al., 2019).

In recent years, there has been a growing interest for the synthesis of nanomaterials due to their wide applicability in many areas, including medicine and biology (Perde-Schrepler et al., 2016). Perde-Schrepler et al. (2016) determined the effect of gold nanoparticles with water extract of CM fruits (GNPs-CM) on human keratinocyte cell lines HaCaT and epidermoid carcinoma cell lines A431 and found that 20 μg/mL of GNPs-CM showed a strong cytotoxic effect in HaCaT cells compared to the A431 cells. The concentrations which reduced the cell population by 50% (IC_{50}) were 23.9 μg/mL for HaCaT cells and 28.19 μg/mL for A431 cells. NP's of gold (AuNPs) stimulated the proliferation of human gingival fibroblasts (HGF) cell lines, a dose-dependent effect up to 50 μg/mL, then viability was decreased. Human Caucasian dysplastic oral keratinocytes (DOK) cells viability was decreased by AuNPs, NP's of silver (AgNPs) and water extract of CM fruits in a dose dependent manner. CM fruits extract showed only a low decrease, at high doses (≥50 μg/mL). AuNPs showed the highest toxicity against DOK cells, since viability was already decreased compared with controls at 10 μg/mL. However, NPs induced cell death through the p53-BAX-BCL-2 pathway, correlated with the inhibition of the antiapoptotic PI3K/AKT/mTOR pathway and BCL-2 protein, leading to necrosis and intrinsic apoptosis (Baldea et al., 2020). NP's showed strong cytotoxic activity compared to fresh and ethanol extract of CM fruits, methanol extract of CM flowers and CM juice. More studies are needed to demonstrate the effects of CM on cancer cells. Also, the toxic effects of CM extracts on both cancer and non-cancer cells should also be evaluated.

4.1.4. Renal protective activity

Only one study revealed the effects of deionized water extract of CM fruits (100 mg/mL) on the renal system using African green monkey kidney epithelial cells-Vero (ATCC, CCL-81), which showed cell viability is 42% in cisplatin treated cells with 50 mg/mL and 59% in cisplatin with 50 mg/mL and deionized water extract of CM fruits with 100 mg/

mL treated cells against cisplatin-induced renal cell injury (Yarim et al., 2017). Also, the deterioration effect of cisplatin decreased in cisplatin and CM treatment.

4.1.5. Hypolipidemic activity

An *in vitro* study conducted by Świerczewska et al. (2019) found that pelargonidin, contains 3-O-galactoside isolated from CM fruits (7.5 mg/mL) are the most active subfraction for the inhibition effect with pancreatic lipase (PL) activity by 28.3 ± 1.5%. This study suggested that CM fruits can inhibit pancreatic enzymes and therefore may be an appropriate food for preventing hyperlipidemia related diseased.

4.2. In vivo studies

In vivo studies have justified the antioxidant biological effect of antioxidant, anti-microbial, hypolipidemic and renal protective effects of CM, exhibited by *in vitro* studies. Apart from these therapeutic effects, the anti-inflammatory, anti-obesity, anti-diabetic, liver-protective, neuroprotective, cardio-protective, hypotensive and anti- glaucoma effects are also evaluated by *in vivo* studies (Table 5).

4.2.1. Anti-diabetic and anti-obesity activities

Diabetes Mellitus (DM) is a complex disease that represents a set of autoimmune, metabolic and genetic disorders that share one major characteristic; hyperglycemia (Turan et al., 2015). Specifically, obesity has a critical role in the development and progression of type 2 diabetes mellitus (T2DM) (Genser, Casella Mariolo, Castagneto-Gissey, Panagiotopoulos, & Rubino, 2016).

Anthocyanins and ursolic acid supplements isolated from CM fruits at the dose of 500 mg/kg bw/d for 8 weeks, decreased serum total triglyceride (TG) and total cholesterol (TC) and increased serum insulin levels in mice. Anthocyanins were more effective than ursolic acid and showed a 24% reduction in body weight (Jayaprakasam et al., 2006). Moreover, Rasoulian, Shahryar, Abbaspour, and Lotfi (2012) showed a significant decrease in fasting blood glucose (FBG) and elevation of insulin levels in diabetic and obese hamsters after 20 days with the treatment of 5 g/d dried CM fruits. Powder lyophilized CM fruits consumption at doses of 500 and 1000 mg/kg bw/d reduced FBG in mice after 12 weeks but did not affect Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). The dose of 1000 mg/kg bw/d consumption especially exhibited a more powerful effect than 500 mg/kg of bw (FBG/insulin ratio: 2.73 ± 0.56 for 500 mg/kg and 2.39 ± 0.41 for 1000 mg/kg) (Capcarova et al., 2019). Similarly, Dzydzan et al. (2019) found ethanol extract of red and yellow CM fruits (20 mg/kg intraperitoneal injection -*i.p.*- for 14 days) reduce FBG (the index of the area under the glycemic curve values were lower in red and yellow CM groups than diabetic group 3 and 2.1-fold, respectively) and increase glucose intolerance. Also, 75% ethanol extract of CM fruits (100 mg/kg bw/d for 3 days) decreased serum glucose (767.82 ± 117.44 mg/dL for diabetic rats, 274.01 ± 45.25 mg/dL for 75% ethanol extract of CM fruits treated rats, 221.83 ± 13.11 mg/dL for glibenclamide treated rats), TG (226.31 ± 15.35 mg/dL, 130.19 ± 29.82 mg/dL, 156.29 ± 12.13 mg/dL,respectively), very low-density lipoprotein (VLDL) (45.29 ± 3.10 mg/dL, 26.03 ± 5.96 mg/dL, 31.25 ± 2.42 mg/dL, respectively), low-density lipoprotein (LDL) (39.04 ± 12.09 mg/dL, 23.98 ± 9.89 mg/dL, 27.25 ± 9.82 mg/dL, respectively) levels and increased high-density lipoprotein (HDL) levels (26.58 ± 6.15 mg/dL, 54.23 ± 12.18 mg/dL, 51.86 ± 9.22 mg/dL, respectively). These effects were similar to glibenclamide treatment (50 mcg/kg *i.p.*) (an anti-diabetic drug), while TG and VLDL reduction by 75% ethanol extract of CM fruits were greater than glibenclamide (Mirbadalzadeh & Shirdel, 2012). Different extracts and components of CM (anthocyanins and ursolic acid supplements isolated from CM fruits, dried CM fruits, powder lyophilized CM fruits, ethanol extract of CM fruits) showed anti-diabetic effects, however more studies are needed to confirm which extract or compound is more effective.

4.2.2. Hypolipidemic activity

Dyslipidemia is an important risk factor for cardiovascular and cerebrovascular diseases and associated complications. Daily consumption of different doses of CM fruits (5, 10 and 15 g/d) for 20 days in hamsters showed a decrease in serum TC (mg/mL: 136.7 for control, 109.2 for 5 g CM, 103,7 for 10 g CM and 108.3 for 15 g CM), LDL (mg/mL: 27.5, 20.3, 20.7, 21.0, respectively) and cortisol (ng/mL: 45.8, 30.3, 34.0, 28.8, respectively), while increasing HDL levels (mg/mL: 51.0, 52.0, 53.6, 54.0, respectively). 10 g/d CM fruits supplement were found to have a more efficient hypolipidemic effect than other doses (Lotfi, Shahryar, & Rasoolian, 2014). Asgary, Rafieian-Kopaei, Shamsi, Najafi, and Sahebkar (2014) found that treatment with either glibenclamide or CM fruits with 2 g/d for 4 weeks exhibited significantly lower serum glucose, TG, LDL, aspartate transaminase (AST), alkaline phosphatase (ALP) and alanine transaminase (ALT) in diabetic rats while showing no significant difference between glibenclaminde and CM fruits (for diabetic control, glibenchlamide and CM treated groups (mg/dL), blood glucose: 316.40 ± 66.56, 105.50 ± 21.09 and 96.72 ± 38.40; TG: 149.60 ± 19.13, 47.66 ± 14.17 and 46.45 ± 19.21; LDL: 25.20 ± 1.64, 21.20 ± 4.65 and 19.12 ± 2.79; AST: 190.40 ± 35.19, 114.16 ± 56.64 and 142.77 ± 57.73; ALP: 1374.80 ± 381.73, 904.40 ± 399.88 and 698.27 ± 270.88; ALT: 69.00 ± 18.37, 53.16 ± 15.03 and 44.22 ± 11.81, respectively). Also, CM fruits treatment showed a less severe hepatic portal inflammation than other study groups. Mirbadalzadeh and Shirdel (2012) showed 75% ethanol extract of CM fruits with the dose of 100 mg/kg bw/d for 3 days decreased serum TG, VLDL and LDL and increased HDL levels in rats (Their values are detailed in Section 4.1.1). In a study by Hosseinpour, Shomali, and Rafieian-Kopaei (2017) different doses of the dried powder of CM fruits (CCDP) (0.25, 0.5, 1, 2 g/100 g bw) supplements were given to rats which showed a reduction in TG and LDL, and increase HDL and liver antioxidant capacity after 4 weeks (for diabetic and 0.25, 0.5, 1, 2 g/100 g bw of CCDP groups (mg/dL); TC: 196.7 ± 35.2, 74 ± 21.7, 55.6 ± 6.10, 88.2 ± 24.0 and 68.1 ± 13.6; LDL: 49.4 ± 12.1, 31.8 ± 0.727, 32.8 ± 2.87, 38.7 ± 7.66 and 36.6 ± 2.81; HDL: 12.9 ± 0.625, 22.7 ± 3.52, 25.9 ± 6.03, 49.5 ± 7.86 and 33.5 ± 3.32, respectively). Gholipour, Shomali, and Rafieian-Kopaei (2018) reported a decrease in VLDL and TG with the consumption of 0.25, 0.5, 1 or 2 g/100 g bw/d CCDP for 4 weeks in rats (for diabetic and 0.25, 0.5, 1, 2 g/100 g bw of CCDP groups (mg/dL); VLDL: 138 ± 48.5, 24.6 ± 8.58, 9.40 ± 2.16, 11.4 ± 3.65 and 8.62 ± 1.65; TG: 694 ± 242, 123 ± 42.9, 47 ± 10.8, 57.2 ± 18.2 and 43.1 ± 8.29, respectively). Moreover, hormone-sensitive lipase (HSL) activity is acutely controlled by reversible phosphorylation which is antagonized by insulin. Therefore, HSL activity increases insulin deficiency which can lead to reduced HSL mRNA and protein expression. This can describe the reduction which was observed in adipose tissue HSL protein levels. Only 1 g/100 g bw/d consumption of CCDP showed a strong increase in HLS levels in adipose tissue (just about > 20 ng/mL compared than diabetic group with 10 ng/mL). Additionally, the consumption of 100 g/kg bw/d lyophilized CM fruits for 60 days reduced 44% serum TG levels and improved the thoracic aorta by decreasing the development of atheromatous changes, while also increasing peroxisome proliferator-activated receptor-α (PPAR-α) levels in liver of hypercholesterolemic rabbits (Sozański et al., 2014). In CM studies which have more focused on its hypolipidemic effect, demonstrated that all dried powder, lyophilized or fresh CM fruits or ethanol extract of CM fruits; consumption may be beneficial to decrease serum lipid levels and act as a therapeutic agent in diseases related to hyperlipidemia which could also be applied in the pharmaceutical industry to develop new therapeutic drugs.

Table 5
Summary of biological activities of *Cornus mas* L. for *in vivo* studies.

Effect	Model	Extract/compound	Dosage	Administration	Results	References
Hypolipidemic Anti-diabetic Anti-obesity	High-fat-fed C57BL/6 mice (n = 32)	Anthocyanins and ursolic acid isolated from CM fruits	500 mg/kg bw/daily for 8 weeks	Oral	Anthocyanins and ursolic acid treated mice elevated glucose intolerance and also showed a significant decrease in liver triacylglycerol concentration. Especially anthocyanins treatment showed more efficiency and mice showed a 24% decrease in weight gain by only anthocyanins treatment.	Jayaprakasam et al., 2006
Antioxidant	Male New-Zealand rabbits (n = 25)	Powder of CM fruits	1 g/kg bw/daily for 60 days	Oral	CM powder significantly increased antioxidant activity in plasma and reduced MDA, fibrinogen and AIP (AIP = log TG/HDL). It also decreased in TC, LDL and TG levels and atherosclerotic lesion in the aorta, but these levels were not statistically significant.	Rafieian-Kopaei et al., 2011
Anti-inflammatory Antioxidant	Type 2 diabetes Sprague Dawley rats (n = 50)	TAM beverage (noni fruit, CM, and olive leaf extract)	2 mL of solutions containing 25%, 50% , or 100% TAM for 25 days	Gavage	TAM beverage treatment showed a decrease in weight gain, FBG levels and AGE's. Also, improved immunity via increased T cell counts and CD^{4+}/CD^{8+} ratio.	West et al., 2012b
Anti-diabetic Anti-obesity	Diabetic and obese hamsters (n = 36)	Dried CM fruits	5, 10 or 15 g/daily for 20 days	Oral	Fed with the dose of 5 g of dried CM only at first daily meal group, showed a significant decrease in FBG and elevate of insulin levels.	Rasoulian et al., 2012
Anti-diabetic	Male rats (n = 40)	75% ethanol extr. of CM fruits	100 mg/kg bw/daily for 3 days	*i.p.*	75% ethanol extract of CM fruits decreased in glucose, TG, VLDL and LDL levels and inceased HDL. These effects were similar to glibenclamide; and TG and VLDL reduction by CM are more effectively than glibenclamide.	Mirbadalzadeh & Shirdel, 2012
Antioxidant	Male Sprague–Dawley and CCI_4-treated rats (n = 18)	80% methanol extr. of CM leaves	500 mg/kg bw/daily for 21 days	Oral	CM treatment group showed an increase SOD, CAT, GPx levels in blood while SOD and GPx levels in liver. These increases were not statistically significant, whereas total antioxidant levels increased statistically significantly in blood and liver.	Celep et al., 2013
Anti-diabetic Hypolipidemic Anti-inflammatory	Healthy and diabetic male rats (n = 28)	CM fruits	2 g/daily for 4 weeks	Oral	Treatment with either glibenclamide or CM showed significant decrease serum glucose, LDL, AST, ALP, ALT and TG in diabetic rats and there was no significant difference between glibenclaminde and CM. Also, CM-treatment exhibit a less severe hepatic portal inflammation than other groups.	Asgary et al., 2014
Hepatoprotective Antioxidant	CCl_4 treated oxidative stress in Wistar albino rats (n = 42)	70% methanol extr. of CM fruits	300 and 700 mg/kg bw/daily for 48 h	*i.p.*	Both doses of methanol extracts of CM significantly increased SOD, catalase, GPx, protein and albumin levels and decreased in urea and uric acid levels. Methanol extracts of CM ameliorated the alterations induced with CCl_4 in lipid peroxidation, antioxidant defenses, biochemical and renal lesions.	Es Haghi et al., 2014
Hypolipidemic	Hamsters (n = 36)	CM fruits	5,10 and 15 g/daily for 20 days	Oral	All doses of CM treatment showed a decrease in TC, LDL and cortisol, and and increase HDL levels. Also, 10 g of CM supplement showed more efficiency hypolipidemic effect than the other doses.	Lotfi et al., 2014
Cordioprotective	Male rats (n = 40)	70% methanol extr. of CM fruits	50, 200 and 400 mg/kg bw/daily for 21 days	Oral	CM treatment decreased in the hemoglobin distribution width and platelet distribution width, but only high doses caused significant increase in the mean corpuscular hemoglobin concentration, mean platelet volume, total platelet mass, and reduce the red cell distribution width.	Abdollahi et al., 2014
Hepatoprotective	CCl_4-induced male rats (n = 30)	70% methanol extr. of CM fruits	200 and 500 mg/kg bw/daily for 14 days	Oral	CM caused significant changes to reduce serum ALT, AST and ALP levels, increase total serum protein and albumin.	Alavian et al., 2014

(*continued on next page*)

Table 5 (*continued*)

Effect	Model	Extract/compound	Dosage	Administration	Results	References
Neuroprotective	Rats (n = 36)	Lyophilized CM fruits	10% of experimental diet	Oral	CM treated rats increased activity of catalase in brain tissue and paraxonase activity in both brain tissue and plasma. In addition, protective effect of CM was observed in the process of oxidation of proteins by decreasing levels of protein carbonyl groups and thiol groups in both brain tissue and plasma.	Francik et al., 2014
Hypotensive	Male Sprague–Dawley rats (n = 20)	LWDHF (mixture with CM fruits)	8.13 g/kg bw/daily for 6 weeks	Oral	LWDHF treatment reduced MAP, FBG, insulin, HDL, TG and angiotensin II from plasma and angiotensin II and rennin from renal. Also, reduced the loss of urinary Na ve K and elevated the glomerular afferent arteriole, arterioles and all renal units.	Yang et al., 2014
Liver protective Renal protective	Wistar rats (n = 40)	70% methanol extr. of CM fruits	50, 200, and 400 mg/kg bw/daily for 3 weeks	*i.p.*	200 and 400 mg/kg of CM treatment showed a decrease in AST, ALT, and ALP in the blood, and all doses of CM reduced GGT, urea, and creatinine. Besides, there were no pathological changes in the liver and renal tissues of the groups.	Abbasi et al., 2014
Hypolipidemic Antioxidant Anti-inflammatory	Hypercholesterolemic rabbits (n = 40)	Lyophilized CM fruits	100 mg/kg bw/daily for 60 days	Oral	CM supplementation reduced 44% serum TG levels and improved thoracic aorta by decreasing development of atheromatous changes. Also, it increased PPAR-α levels in liver.	Sozański et al., 2014
Anti gloacuma	New Zealand rabbits (n = 14)	Loganic acid isolated from CM fruits	0.7% loganic acid solution for 5 h	*i.p.*	It was found significant IOP-hypotensive effect at 1,2,3 and 5 h after loganic acid treatment. Loganic acid showed approximately a 25% decrease in IOP within the first 3 h of treatment. Moreover, 0.7% solution of loganic acid caused strong effect on IOP compared to widely ophthalmologically used drug, timolol.	Szumny et al., 2015
Anti-inflammatory	Male Wistar rats with paw inflammation (n = 32)	AECM	15 or 30 mg/kg bw/daily 2 doses for 5 days	Oral gavage	AECM reduced TNF-α, IL-1β, IL-13 levels as well as increase IL-10 levels. 15 g/kg bw of AECM showed a decrease in acute inflammatory reaction while 30 g/kg bw of AECM showed inhibition effect of exudation of inflammatory cells to the inflammation site.	Moldovan et al., 2016a
Anti-inflammatory Hypolipidemic	Hypercholesterolemic rabbits (n = 40)	Loganic acid and anthocyanins isolated from CM fruits	20 mg/kg bw/daily loganic acid or 10 mg/kg of bw/daily anthocyanins for 60 days	Oral	Both treatment of loganic acid and anthocyanins decreased in LDL levels, whereas increased PPAR-α and PPAR-γ expression. Loganic acid significantly decreased in TNF-α and IL-6, while anthocyanin moderately decreased in IL-6 and did not significantly affect TNF-α levels.	Sozański et al., 2016
Hypolipidemic Neuroprotective	Male Wistar rats (n = 54)	CM juice	10% of experimental diet for 5 weeks	Oral	CM juice did not significantly effect the change in the activity of PON1.	Francik et al., 2017
Antioxidant Anti-inflammatory	Hypercholesterolemic New Zealand rabbits (n = 40)	Lyophilized CM fruits	100 mg/g bw/daily for 60 days	Oral	CM treatment increased the L-arginine and L-arginine/ADMA ratio and DDAH activity, reduce ADMA and SDMA. Incresed DDAH activity effect redox state in aorta, but not in blood with a decrease in MDA, and increase glutathione, GPx and SOD. In addition, CM treatment showed a significant decrease in intima thickness and the intima/media ratio in thoracic aorta.	Sozański et al., 2017
Antioxidant	Wistar rats (n = 60)	CM fruits	2.5, 5, 10 mg/kg bw/daily for 1 time	*i.p.*	10 mg/kg bw of CM decreased in the frequency of epileptiform activity and MDA levels in erythrocytes and increased xanthine oxidase levels in plasma.	Tubas et al., 2017
Hypolipidemic	Wistar rats (n = 48)	CCDP	0.25, 0.5, 1 or 2 g/100 g bw/daily for 4 weeks	Oral	All doses of CCDP treated rats showed a decrease in LDL, TC, and increase HDL and liver antioxidant capacity, while no significant changes on serum glucose. Only 1 g/100 g bw of CCDP treatment decreased in HMG-CoA reductase levels.	Hosseinpour et al., 2017

(*continued on next page*)

Table 5 (*continued*)

Effect	Model	Extract/compound	Dosage	Administration	Results	References
Hypolipidemic	Male adult rats (n = 56)	CCDP	0.25, 0.5, 1 or 2 g/100 g bw/daily for 4 weeks	Oral	CCDP and fenofibrate treatment reduced TG and VLDL. The doses of 0.25, 1 and 2 g/100 g CCDP decreased in serum AST and; all doses (except 1 g/100 g) of CCDP increased LPL levels. Only 1 g/100 g CCDP treatment showed a significant increase in HLS levels in adipose tissue.	Gholipour et al., 2018
Anti-inflammatory	T.spiralis-infected mice (n = 60)	CM fruits	100 mg/kg bw/daily for six times within a period encompassing three days prior to the infection and three days after the infection (days)	Oral	CM treatment after 5 days, increased the percentage of CD^{3+},CD^{4+} cells and CD4 + / CD^{8+} and decreased total amount of CD^{8+} and CD^{19+} splenocytes. After 7 days, it increased the percentage of CD^{4+} cells and CD^{4+}/ CD^{8+} ratio after 21 days. Moreover, CM treatment showed a significant increase leukocyte with red blood cells.	Piekarska et al., 2018
Antioxidant	Hypercholestorelomic New Zealand rabbits (n = 40)	Loganic acid and antyhocyanins isolated from CM fruits	20 mg/kg bw/daily loganic acid or 10 mg/kg of bw/daily anthocyanins for 60 days	Oral	Both loganic acid and anthocyanins decreased the formation of atherosclerotic plaques in the aorta. Both of them showed a decrease in MDA, while increase GPx and GSH levels.	Sozański et al., 2018
Anti-diabetic Antioxidant	Type 1 diabetes rats (n = 36)	80% ethanol extr. of red or yellow CM fruits	20 mg/kg bw/daily for 14 days	Oral	Both CM treatment decreased in FBG and increased glucose intolerance.	Dzydzan et al., 2019
Anti-diabetic	Zucker diabetes rats (n = 40)	Lyophilized CM fruits powder	500 or 1000 mg/kg bw/daily for 12 weeks	Gastric gavage	CM showed a significant decrease in FBG, especially at the dose of 1000 mg/kg. However, both doses did not significantly effect HOMA-IR. Also, CM showed a restriction of water intake.	Capcarova et al., 2019
Anti-inflammatory Antioxidant	Wistar rats (n = 40)	AuNPs-CM and AgNPs-CM	15 mg bw/d of water extr. of CM fruits or 0.3 mg bw of gold or silver nanoparticles with water extr. of CM fruits for 4 consecutive days, prior to injection of carrageenan injection	Oral	AgNPs-CM and AuNPs-CM decreased IL-1α, IL-1β, IL-6 and MCP-1 mainly early after induction of inflammation. Also, they diminished inflammation and apoptosis in the early stage while later, at 48 h, exerted an immunomodulatory effect, activated ERK 1/2 and induced apoptosis.	Filip et al., 2019
Cytotoxic	Female BALB/c mice (n = 20)	CM juice	100 μg/L/daily for 10 days	Oral gavage	CM juice treatment did not inhibit tumor cells.	Tiptiri-Kourpeti et al., 2019
Antioxidant Anti-inflammatory	Hypercholestorelomic New Zealand rabbits (n = 40)	Loganic acid and antyhocyanins isolated from CM fruits	20 mg/kg bw/daily loganic acid or 10 mg/kg of bw/daily anthocyanins for 60 days	Oral	Both loganic acid and anthocyanins increased L-arginine levels, L-arginine/ADMA ratio; and in thoratic aortas, increased mRNA expression of eNOS, however only anthocyanins increased DDAH levels in liver.	Sozański et al., 2019
Anti-inflammatory	Wistar rats (n = 40)	70% methanol extr. of lyophilized CM fruits	300 or 700 mg/daily for 16 days	Oral	Both doses increased SOD, GPx and total antioxidant capacity which are decreased by cisplatin. Also, they decreased MDA levels and ameliorated liver enzymes (AST and ALP).	Abbasi et al., 2020

*The table is sorted by year; mg, miligram; kg, kilogram; mL, mililiter; extr, extract; bw, body weight; LWDHF, Liu-Wei-Di-Huang-Fang; AECM, acetone extract of CM fruits; CCDP, CM fruits dried powder; AuNPs-CM, gold nanoparticles with water extr. of CM fruits; AgNPs-CM, silver nanoparticles with water extr. of CM fruits; *i.p.*, intraperitoneal injection; MDA, malondialdehyde; AIP, log TG/HDL; LDL, low-density lipoprotein; TG, triglycerides; FBG, fasting blood glucose; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GSH, reductase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; ALT, alanine transaminase; TC, total cholesterol; Na, sodium; K, potassium; GGT, gamma-glutamyl transferase; IOP, intraocular pressure; PPAR-α, peroxisome proliferator-activated receptor α; PPR-γ, peroxisome proliferator-activated receptor-γ; AGE, advanced glycation end products; HLS, hormone-sensitive lipase; LPL, lipoprotein lipase; HOMA-IR, homeostatic model assessment of insulin resistance; mRNA, messenger RNA; eNOS: endothelial nitric oxide synthase; ERK1/2, p44/42MAP Kinase; CCI_4, carbon tetrachloride; MAP, mean arterial pressure; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β, IL-1α; interleukin-1α; IL-13, interleukin-13; IL-6, interleukin-6; PON1, paraoxonase 1; ADMA, Asymmetric dimethyl arginine; DDAH, Dimethylarginine dimethylaminohydrolase; SDMA, Symmetric dimethylarginine; HMG-coA: 3-hydroxy-3-methyl-glutaryl-CoA reductase; MCP-1, monocyte chemoattractant protein-1.

4.2.3. Cardioprotective and antioxidant activities

Cardiovascular disease (CVD) is a general term for conditions affecting the heart or blood vessels. CVD are usually related to the accumulation of fatty deposits inside the arteries (atherosclerosis) along with an increased risk of blood clots. Fibrinogen, an inflammatory protein, can restore homeostasis and reduce the inflammation which has an important role in the process of atherosclerosis and other CVD (Chen et al., 2018). CM fruits powder at the tested dose of 1 g/kg bw/d for 60 days significantly increased antioxidant activity (3.16 ± 0.74 in high fat diet (HFD) and 48.34 ± 12.39 in HFD + CM group) in plasma and reduced malondialdehyde (MDA) (0.45 ± 0.06 and 0.24 ± 0.03, respectively), fibrinogen (253 ± 10.5 and 223 ± 18.16, respectively) and AIP (AIP = log TG/HDL) in rabbits. It also decreased in serum TC (1676 ± 585.2 and 2224 ± 450.6, respectively), LDL (1370 ± 256 and 1028 ± 66.36, respectively) and TG (772 ± 199.93 and 458 ± 47.47, respectively) levels, in addition to decreasing atherosclerotic lesion in the aorta, although these levels did not demonstrate statistical significance (Units are not given in the article) (Rafieian-Kopaei et al., 2011). MDA, an end product of unsaturated fatty acid peroxidation, is an indicator for antioxidant power and lipid peroxidation (Pieme et al., 2017). Tubas et al. (2017) showed that after the consumption of 10 mg/kg bw of CM fruits, showed a reduction in the frequency of epileptiform activity and MDA levels (24.488 ± 0.78 nmol/g Hgb) in erythrocytes and an increase of xanthine oxidase (XO) levels (354.75 ± 33.82 μU/mL) in the plasma of rats. Similarly, both loganic acid (20 mg/kg bw/d) and anthocyanins (10 mg/kg bw/d) isolated from CM fruits reduced the formation of atherosclerotic plaques in the aorta. They both showed a decrease in MDA, while increase glutathione peroxidase (GPx) and glutathione reductase (GSH) levels in rabbits (for cholesterol and cholesterol + loganic acid/ anthocyanins treated groups; MDA (μM/mg) 100 and between 60 and 80; GSH (mM/mg): between 6–9 and 9–12; GPx (U/mg): 10 and between 10 and 15, respectively) (Sozański et al., 2018).

Consumption of CM fruits (100 g/kg bw/d) for 60 days improved the thoracic aorta by decreasing the development of atheromatous changes. It also showed that CM increase PPAR-α levels in liver of hypercholesterolemic rabbits (Sozański et al., 2014). In another study, rabbits treated with loganic acid (20 mg/kg bw/d) and anthocyanins (10 mg/kg bw/d) isolated from CM fruits for 60 days reduced LDL levels, while increase PPAR-α and peroxisome proliferator-activated receptor-γ (PPR-γ) expression. Anthocyanins and loganic acid increased PPAR-γ levels by 193% and 67.6%; PPAR-α levels by 123% and 85.2%, respectively. Loganic acid treatment showed a significant decrease in tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), while anthocyanins moderately decreased in IL-6 and did not significantly affect TNF-α levels (Sozański et al., 2016). The authors indicated that the protective effect of CM against diet-induced hypercholesterolemia may increase through PPAR-α protein expression and via-regulating oxidative stress and inflammatory processes. In addition, 100 mg/g bw/d of CM fruits treatment for 60 days exhibited an increase in L-arginine (just about 120 μmol/L at 0 days and between 120 and 150 μmol/L after 60 days treatment), L-arginine/asymmetric dimethyl arginine (ADMA) ratio (between 120–150 and 150–180, respectively) and dimethylarginine dimethylaminohydrolase (DDAH) activity ((mM L-citruline/g protein/min): between 0.2–0.4 and 0.4–0.6, respectively) along with a decrease in ADMA and symmetric dimethylarginine (SDMA) levels. Increased DDAH activity had an effect on the redox state in the aorta, but not in blood where a decrease in MDA, and increase glutathione, GPx and superoxide dismutase (SOD) are seen. Also CM treatment showed a significant reduction in the intima thickness and the intima/media ratio in the thoracic aorta in hypercholesterolemic rabbits (Sozański et al., 2017). Similarly, loganic acid (20 mg/kg bw/d) and anthocyanins (10 mg/kg bw/d) isolated from CM fruits for 60 days increased L-arginine levels, L-arginine/ADMA ratio in plasma (for cholesterol-treated group and cholesterol + loganic acid/anthocyanins treated group; L-arginine: just about 150 and 200 μmol/L; L-arginine/ADMA ratio: just about 100 and between 150 and 200); and in thoracic aorta, increased mRNA expression of endothelial nitric oxide synthase (eNOS) (just about 0.5 RQ and between 1.5 and 2 RQ, respectively), however only anthocyanins increased DDAH levels (between 0.2–0.3 and 0.3–0.4 mM L-citruline/g protein/min, respectively) in the liver of hypercholesterolemic rabbits (Sozański et al., 2019). Different doses of 70% methanol extract of CM fruits (50, 200 and 400 mg/kg bw/d) treatment for 21 days, reduced the hemoglobin and platelet distribution width, but only high doses caused significant increase in the mean corpuscular hemoglobin concentration, mean platelet volume, total platelet mass, and a decrease in the red cell distribution width (Abdollahi et al., 2014). According to the literature, fresh and methanol extract of CM fruits; loganic acid and anthocyanins isolated from CM fruits can exhibit a strong protective effect against atherosclerosis. As you can see, CM is a superb plant for treatment of CVD and complications.

4.2.4. Anti-inflammatory activity

A study showed a Thrive Adaptogenics Max (TAM) beverage (a pasteurized beverage containing noni fruit, CM fruit and olive leaf extract) treatment with 2 mL of solutions containing 25% (low dose), 50% (mid dose), or 100% (high dose) TAM beverage for 25 days, lead to a decrease in weight gain, FBG levels ((mmol/L): 12.1 ± 0.58 for diabetic, 11.3 ± 0.91 for low dose, 10.7 ± 0.68 for mid dose, and 10.2 ± 0.55 high dose group) and advanced glycation end-products (AGEs) ((pg/mL): 36.9 ± 4.67, 32.7 ± 4.26, 31.4 ± 4.32, 30.1 ± 5.19, respectively) depending on the dose. It also demonstrated improved immunity via increased T cell counts and CD^{4+}/CD^{8+} cells ratio (0.75 ± 0.254, 0.91 ± 0.301, 1.13 ± 0.229 and 1.43 ± 0.512) in type 2 diabetic rats (West, Ma, Deng, Jensen, & Su, 2012b), hence iridoid-rich beverage may help reduce the negative health effects associated with the aging process. Consuming doses at 100 mg/kg bw/d CM fruits treatment after 5 from T.spiralis infection, increased the percentage of CD^{3+} (34.3 ± 3.25 for infected group and 40.7 ± 4.42 for CM treated group), CD^{4+} (23.5 ± 4.54 and 29.4 ± 3.49, respectively) cells and CD^{4+}/CD^{8+} (3.5 ± 0.53 and 4.9 ± 0.89, respectively) and decreased in the amount of CD^{8+} (6.7 ± 1.11 and 6.3 ± 1.57, respectively) and CD^{19+} (61.8 ± 4.89 and 56.7 ± 4.78, respectively) splenocytes. It increased the percentage of CD^{4+} cells (28.3 ± 5.26 and 33.0 ± 6.81, respectively) after 7 days and CD^{4+}/CD^{8+} ratio (4.0 ± 0.77 and 4.9 ± 0.89, respectively) after 21 days. Moreover, CM fruits treatment showed a significant increase in leukocytes and red blood cells levels in infected mice (Piekarska, Szczypka, Kucharska, & Gorczykowski, 2018). Moldovan et al. (2016a) stated that administration of the acetone extract of CM fruits (AECM) with 15 or 30 mg/kg bw/daily 2 doses for 5 days led to a reduction of TNF-α, interleukin-1β (IL-1β), interleukin-13 (IL-13) levels as well as increase of interleukin-10 (IL-10) levels in rats with paw inflammation. The dose of 5 g/kg of AECM showed a decrease in acute inflammatory reaction while 30 g/kg of AECM showed an inhibition of exudate in inflammatory cells at the inflammation site in these rats. Additionally, 0.3 mg bw of AgNPs-CM and AuNPs-CM for 4 consecutive days, prior to a carrageenan injection, decreased IL-1α, IL-1β, IL-6 and monocyte chemoattractant protein-1 (MCP-1). This occurred early after the induction of inflammation effect which persisted to a lesser extent at 48 h in rats with carrageenan, in paw tissue. Inflammation and apoptosis diminished in the early stage while at 48 h, exerted an immunomodulatory effect, activated p44/42MAP Kinase (ERK 1/2) and induced apoptosis (Filip et al., 2019). Fresh and acetone extract of CM fruits, CM fruits containing beverages which contain gold and silver NP's with water extract of CM fruits showed anti-inflammatory activity. Additional studies are needed to determine whether different extracts of CM fruits are more effective.

4.2.5. Liver and renal protective activities

Dietary 70% methanol extract of CM fruits consumption with the

doses of 200 and 500 mg/kg of bw/d for 14 days caused a significant decrease in elevated serum level of enzymes (AST, ALT and ALP) and increased total serum protein and albumin levels in carbon tetrachloride (CCl_4-) induced rats ((U/L): AST, 155.74 ± 4.21 for carbon tetrachloride (CCl_4-) induced rats, 101.82 ± 4.69 for 200 mg/kg CM + CCl_4 rats, and 115.03 ± 2.96 for 500 mg/kg CM + CCl_4 rats; ALT, 197.4 ± 5.05, 133.60 ± 5.59 and 116.87 ± 5.65; ALP, 322.63 ± 10.98, 248.97 ± 6.11 and 235.23 ± 5.24, respectively; and g/dL: total protein, 5.83 ± 0.23, 7.10 ± 0.11 and 7.25 ± 0.14; albumin, 1.31 ± 0.08, 2.20 ± 0.09 and 2.85 ± 0.12, respectively) (Alavian, Banihabib, Es Haghi, & Panahi, 2014). 70% methanol extract of lyophilized CM fruits (300 or 700 mg/d for 16 days) increased SOD, GPx and total antioxidant capacity (TAC) levels which are decreased by cisplatin (control, cispatine + 300 and 700 mg/d CM groups; SOD: 36.36, 37.61 and 31.64 U/mL; GPx: 71, 63 and 62 U/mL/100; TAC: 170, 171 and 173 μmol trolox equivalent/mL, respectively) while also showing a decrease in MDA (9.88 nmol/mL for control group; 8.06 and 8.62 nmol/mL for cispatine + 300 and 700 mg/d CM groups) and ameliorated liver parameters (AST and ALP) (control, cispatine + 300 and 700 mg/d CM groups; AST (U/L): 190.67, 185.17 and 185.00; ALP (U/L): 469.67, 328.83 and 331.60, respectively) in rats (Abbasi et al., 2020). These results showed that lyophilized CM fruit supplements could protect from the adverse effects of liver diseases. Alternatively, another study where doses administered at 200 and 400 mg/kg bw/d 70% methanol extract of CM fruits, reduced serum levels of AST, ALT, and ALP in blood after 3 days of treatment (Placebo, 200 and 400 mg/kg bw of CM groups; AST (IU/L): 292.26 ± 28.26, 193.00 ± 3.33 and 160.00 ± 9.63; ALT (IU/L): 98.82 ± 10.26, 67.50 ± 3.52 and 55.56 ± 2.64; ALP (IU/L): 340.18 ± 32.46, 305.50 ± 22.89 and 279.13 ± 21.45, respectively). All doses of 70% methanol extract of CM fruits (50, 200 and 400 mg/kg bw/d) lead to a decrease in serum gamma-glutamyl transferase (GGT), urea, and creatinine (for placebo, 50, 200 and 400 mg/kg bw of CM groups; GGT (IU/L): 12.20 ± 3.88, 8.33 ± 0.56, 7.29 ± 0.47 and 5.14 ± 0.55; urea (mg/dL): 55.68 ± 1.83, 46.83 ± 2.82, 41.71 ± 1.92 and 33.29 ± 1.14; creatinin (mg/dL): 3.69 ± 0.24, 2.31 ± 0.21, 1.15 ± 0.12 and 1.00 ± 0.12, respectively). No pathological changes in the liver and renal tissues of the groups were observed (Abbasi, Abdollahi, Milani, Mohajeri, & Nourdadgar, 2014). Doses of 300 and 700 mg/kg bw/d of methanol extract of CM fruits significantly increased SOD, catalase, GPx, protein and albumin levels while decreasing urea and uric acid levels. The methanol extract of CM fruits, ameliorated the alterations induced with CCl_4- in lipid peroxidation, antioxidant defenses, biochemical and renal lesions in CCl_4- induced rats (Es Haghi et al., 2014). According to studies methanol extract of lyophilized and fresh CM fruits have antioxidant effect which showed protective activity of liver and renal tissues.

4.2.6. Neuroprotective activity

Many people suffer from free radical induced neurological disorders due to the high sugar and fat content of foods consumed. Brain tissue is susceptible to oxidative stress due to the high demand for energy (Francik et al., 2014). Studies evaluated the effect of lyophilized CM fruits or CM juice in 3 types of diets: control, fructose and high fat diets. The result revealed that lyophilized CM fruit treated rats (10% of diet), demonstrated an increase in the activity of catalase which is an antioxidant enzyme, in brain tissue and paraxonase activity in both brain tissue and plasma. In addition, the protective effect of lyophilized CM fruit was observed in the process of oxidation of proteins by decreasing levels of protein carbonyl groups and thiol groups in both brain tissue and plasma (Francik et al., 2014). The increase of paraoxonase 1 (PON1) activity has a protective effect with regard to the LDL fraction and prevents its oxidation caused by oxidative stress. Because, PON1 is an enzyme that plays a role in protecting against oxidation, among other things, two fractions of cholesterol; LDL and HDL provide hydrolysis of activated phospholipids and lipid peroxides (Francik, Kryczyk-Kozioł, Krośniak, & Francik, 2017). PON1 activity reduced by CVD (Kumar & Rizvi, 2014), insulin resistance (Gomathi et al., 2018) and acute infection diseases (Kiratli et al., 2014). In another study, rats treated with 10% CM juice for 5 weeks increased PON1 levels in plasma, but not in liver, however the results were not statistically significant (Francik et al., 2017). Although studies on neuroprotective activity are quite limited, lyophilized CM fruits may be considered to be is rather effective.

4.2.7. Anti-hypertensive activity

Many antihypertensive agents are available to help control blood pressure while ameliorating the quality of life of patients with hypertension. Hypertension is linked with the sympathetic nervous system disorders, anomalies in the renin-angiotensin-aldosterone system, insulin resistance, renal damage, and metabolic abnormalities (Chamarthi, Williams, & Williams, 2010). Yang, He, and Wang (2014) determined treatment with Liu-Wei-Di-Huang-Fang (LWDHF) (8.13 g/kg bw), a compound including rehmannia root (27.2 g), Asiatic cornelian cherry fruit (7.2 g), common yam rhizome (16.4 g), oriental water plantain rhizome (16.4 g), Indian bread (16.4 g) and tree peony root bark (16.4 g), lead to a decrease in mean arterial pressure (MAP), FBG (5.55 ± 0.62 versus 3.61 ± 0.65 mmol/L), insulin (4.92 ± 1.34 versus 3.59 ± 0.39 mIU/L), HDL (0.35 ± 0.20 versus 0.26 ± 0.13 mmol/L), TG (0.54 ± 0.30 versus 0.47 ± 0.21 mmol/L) and angiotensin II from plasma and angiotensin II and rennin from renal after 6 weeks in rats. It also reduced the loss of urinary Na and K and elevated the glomerular afferent arteriole, arterioles and all renal units. It is known that angiotensin converting enzyme (ACE) inhibitors are used in the treatment of hypertension. The results of the study are promising for blood pressure treatment.

4.2.8. Anti-glaucoma activity

Glaucoma is a disease of which there is a significant increase in intraocular pressure (IOP), which can lead to blindness, especially in older individuals (Bulat, Cusnir, Procopciuc, Cusnir, & Cusnir, 2020). The concentration of 0.7% loganic acid isolated from CM fruits showed a significant IOP-hypotensive effect at 1,2,3 and 5 h after treatment. Data revealed an approximate 25% reduction in IOP within the first 3 h of administration. Moreover, 0.7% loganic acid solution caused a strong effect on IOP compared to Timolol, a widely used ophthalmological drug (Szumny et al., 2015). It could also be beneficial for improved vascular flows in diabetic and hypertensive retinopathy or other conditions of ocular blood vessels (e.g., venous thrombosis or arterial embolism).

4.2.9. Cytotoxic activity

Only one study was found to evaluate the cytotoxic effect of CM where 100 μg/L dose of CM juice treatment did not inhibit CT26 colon cancer cells after 10 days in mice (Tiptiri-Kourpeti et al., 2019). This results may be due to the short-term experiment period or the administration dose of CM juice. In addition, *in vitro* studies showed the opposite results compared to *in vivo* mechanism of action, more studies are needed.

4.3. Clinical studies

To date, there are 3 clinical studies evaluating the effect of CM supplements. Asgary et al. (2013) investigated the effects of CM fruits supplementation (50 g × 2 times a day) on lipid profile and vascular inflammation in 40 dyslipidemic children and adolescents. Although CM supplementation leads to a decrease in TC (225.85 ± 56.02 versus 197.14 ± 40.10 mg/dL) TG (137.38 ± 46.51 versus 120.47 ± 50.56 mg/dL), LDL (229.00 ± 57.28 versus 206.20 ± 39.78 mg/dL), apolipoprotein B (Apo B) (86.93 ± 27.48 versus 75.13 ± 19.89 mg/dL), intracellular adhesion molecule-1 (ICAM-1) (105.67 ± 23.16 versus 73.84 ± 16.97 ng/mL) and

Table 6
Summary of biological activities of *Cornus mas* L. for clinical studies.

Effects	Model	Extract/compound	Dosage	Results	References
Anti-inflammatory Hypolipidemic	Dyslipidemic children and adolescents (n = 40)	CM fruits	50 g/daily 2 doses for 6 weeks	CM supplementation decreased in TC, TG, LDL, Apo B, ICAM-1 and VCAM-1, and increased HDL and Apo A1, but only Apo A-1 and ICAM-1 were significantly difference.	Asgary et al., 2013
Anti-diabetic Hypolipidemic	T2DM patients (n = 60)	Anthocyanins extract of CM fruits in the form of capsules	2 capsules/daily 2 doses (300 mg anthocyanins/1doses) for 6 weeks	CM capsule treatment showed an increase the level of insulin, however a decrease in HbA1c and TG levels was observed.	Soltani et al., 2015
Anti-diabetic Anti-obesity	Postmenopausal women (n = 84)	CM fruit extract	300 mg CM fruits extract/daily 3 doses for 8 weeks	CM fruit extract supplementation reduced body weight, BMI, WC, LDL/HDL ratio, TC/HDL ratio and fibrinogen, whereas increased HDL and Apo A levels.	Gholamrezayi et al., 2019

*The table sorted by year; T2DM, type 2 diabetes mellitus; g, gram; TC, total cholesterol; TG, total triglyceride; LDL, low density lipoprotein; Apo B, apolipoprotein B; ICAM-1, intracellular adhesion molecule-1; VCAM-1: vascular cell adhesion protein 1; HDL, high density lipoprotein; Apo A1, apolipoprotein A1; Apo A, apolipoprotein A; HbA1c, hemoglobin A1c; BMI, body mass index; WC, waist circumference.

vascular cell adhesion protein-1 (VCAM-1) levels (1275.35 ± 579.70 versus 948.23 ± 371.26 ng/mL), while increasing HDL (30.70 ± 12.07 versus 36.85 ± 14.51 mg/dL) and apolipoprotein A1 (Apo A1) (151.33 ± 20.48 versus 168.93 ± 17.34 mg/dL) levels are observed. Among the groups, only Apo A1 and ICAM-1 were significantly different. Additionally, no significant difference in body mass index (BMI), waist-to-hip ratio, C-reactive protein was found between the groups. This may be due to the small number of participants and the shorter duration of CM supplementation. Soltani, Gorji, Asgary, Sarrafzadegan, and Siavash (2015) conducted a study of 60 adult individuals with T2DM, that was randomly divided into 2 groups; a treatment group and placebo. The treatment group received the anthocyanins extract of CM fruits in the form of capsules administered after the main meal (1 capsule contains 150 mg anthocyanins, subjects were treated with 2 capsules twice daily) while the placebo group was given for 6 weeks. After 6 weeks of treatment, the CM treated group showed a significant increase in serum insulin levels (1.13 ± 1.90 versus −0.643 ± 1.82) and a decrease in Hemoglobin A1c (HbA1c) (−0.24 ± 0.429 versus 0.023 ± 0.225) and TG (−23.66 ± 55.40 versus 2.83 ± 15.71) levels. These findings suggested that the consumption of the anthocyanin extracts of CM as food supplement may improve the glycemic disorder/glucose intolerance in T2DM patients by increasing the insulin level subsequently reducing the TG and HbA1c levels. In a study by Gholamrezayi et al. (2019) the effect of CM fruits extract on lipid profiles, blood glucose, and leptin parameters in postmenopausal women were studied. Participants were randomly divided into 2 groups. 300 mg of CM fruits extract were given three times a day in one group, and placebo for 8 weeks. After 8 weeks, body weight (74.81 ± 1.87 versus 74.12 ± 1.81), BMI (30.81 ± 0.73 versus 30.54 ± 0.71), waist circumference (107.28 ± 1.70 versus 105.07 ± 1.56), LDL/HDL ratio (2.29 ± 0.09 versus 2.13 ± 0.08), TC/HDL ratio (3.89 ± 0.14 versus 3.63 ± 0.11) and fibrinogen (270.45 ± 17.4 versus 267 ± 17.17) decreased. Also, CM supplementation increased HDL (48.76 ± 1.29 versus 50.64 ± 1.16) and Apo A1 (104.22 ± 3.16 versus 107.85 ± 3.23) levels compared to the control group, however, no change in leptin levels, FBG, serum insulin, insulin resistance index, and insulin sensitivity between the groups were seen, although the FBG levels in both groups decreased. The study revealed that daily consumption of CM fruits may help decrease anthropometric measurements, blood sugar parameters, and lower the risk of CVD (Table 6). Some major biological activities are given in Fig. 1.

In addition, Sangsefidi et al. (2019) published a study protocol in 2019 where they would evaluate the effect of anthocyanin-base standardized CM extract supplementation on liver function in non-alcoholic fatty liver disease (NAFLD) patients. Their study included 80 NAFLD patients divided randomly into 2 groups: 320 mg/daily anthocyanin or placebo for 12 weeks. After treatment serum levels of AST, ALT, cytokeratin 18-M30 (CK-18 M30), TNF-α, MDA, and adiponectin between groups were compared. This study protocol is important since it has been shown in studies that there is an inverse relationship between polyphenol consumption and NAFLD. For example, in a study using food consumption records, phenolic acid intake was found to be correlated with low NAFDL presence (Salomone et al., 2020). In NAFLD patients who received 500 mg resveratrol supplementation for 12 weeks showed a reduction in ALT, inflammatory cytokines, nuclear factor κB activity, CK-18 M30, and hepatic steatosis grade, as compared with placebo supplementation (Faghihzadeh, Adibi, Rafiei, & Hekmatdoost, 2014). In the study by Chen et al. (2015), capsule supplementation containing 150 mg resveratrol once a day for 3 months decreased AST, ALT, FBG, LDL, TC, HOMA-IR, TNF-α and CK-18 M30 levels in NAFLD patients. In another study, in NAFLD patients who took 250 mL of pomegranate (Punica granatum) juice or orange juice supplement for 12 weeks, AST and ALT levels decreased as a result of both supplements, and TAC increased as a result of pomegranate supplementation (Ekhlasi, Shidfar, Agah, Merat, & Hosseini, 2015). Clinical

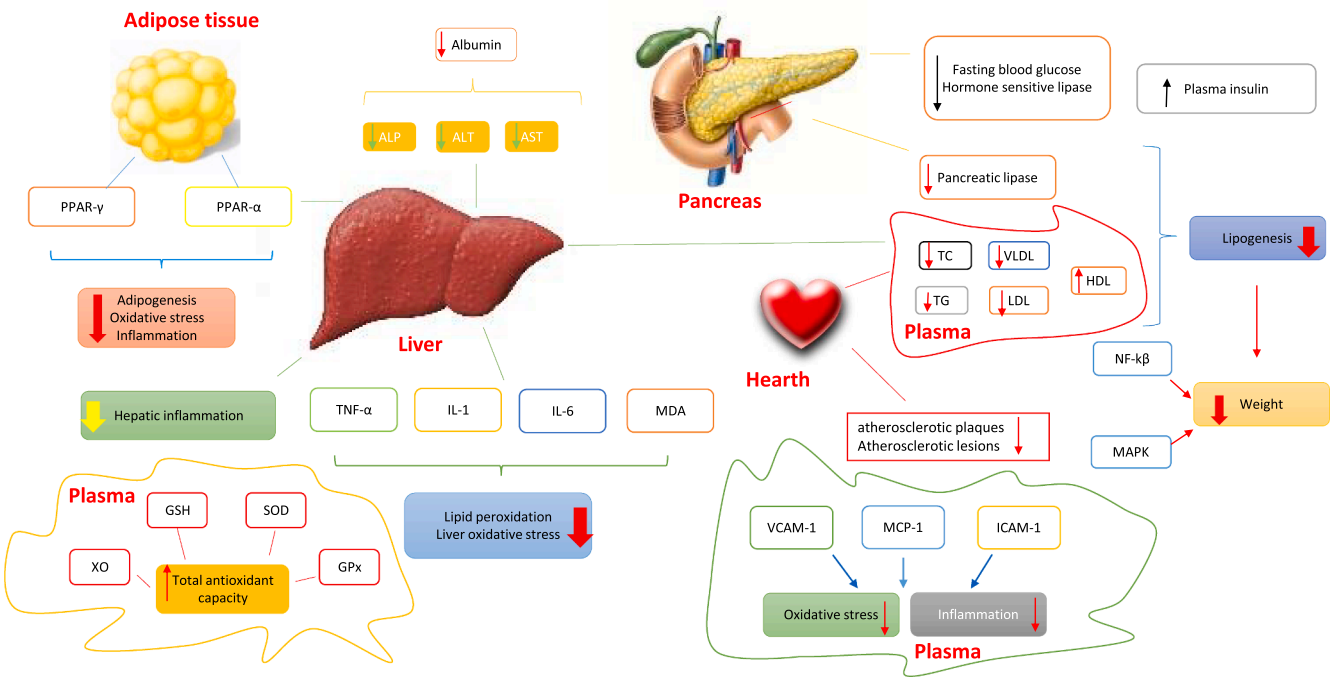

Fig. 1. Anti-obesity, anti-diabetes, hypolipidemic, liver and cardioprotective activities of Cornus mas L. and its metabolites through reduced lipogenesis, levels of TG, TC, LDL, VLDL, MDA, ICAM-1, MCP-1, VCAM-1, liver enzymes, hyperglycemia, plasma insulin, fasting blood glucose level and weight; increased plasma insulin, antioxidant enzymes, HDL, PPAR-α and PPAR-γ levels.

studies on the effect of polyphenols on NAFLD patients are increasing daily, while the results are positive for therapeutic treatment purposes in NAFLD patients. CM fruits appears to be promising treatment in NAFLD patients.

4.4. Toxicity studies

Acute toxicity of CM has been studied in both animal and human models. 5 mL/kg bw of pure CM supplementation for 14 days in rats showed no adverse effect and average lethal dose (LD_{50}) value was evaluated to be < 5200 mg/kg (West et al., 2012a). Similarly, 100–1650 mg/kg doses of water extract of CM fruits supplementation for 2 weeks in mice showed no toxicity and LD_{50} value was determined 1270 mg/kg (Es Haghi et al., 2014). In human studies, 100 g/day doses of fresh CM fruits consumption for 6 weeks did not show any toxicity (Asgary et al., 2013). Therefore, 100 g/day CM fruits consumption is safe for humans. Also, administration of anthocyanins isolated from CM of 600 mg/day doses to adult diabetic patients for 6 weeks did not show any adverse effect (Soltani et al., 2015). Toxicity studies have shown CM consumption is safe and has no side effect, but high doses and long-term toxicity studies are required for CM to be considered a herbal drug.

5. Conclusion

Although the wild fruit, CM, has been used in folk medicine since ancient times, scientific studies of the plant have only intensified since 2009. Studies of the plant's properties have gained in popularity almost 3 fold since 2019. The reported bioactive components of CM. as mentioned in this review suggest that it may contribute to a healthy diet as a "super food" due to it's phenolic components, organic acids, natural sweetness, vitamin C, pectins, carotenoids and essential minerals. It has been used in the treatment of various diseases since ancient times for its anti (-oxidant, -microbial, -diabetic, -atherosclerosis, -obesity, -glaucoma); (cyto-, neuro-, cardio-, liver-, renal-) protective and; hypo (-lipidemia and -tensive) effects. These effects have been partially corroborated via *in vitro* and *in vivo* studies. However, clinical studies are quite limited to prove these effects. Therefore, large-population and long-term clinical studies need to evaluate the biological effects of CM.

6. Ethics statement

Authors declare that neither human nor animal experimentations were included in the paper

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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