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Cornelian Cherry (*Cornus mas* L.): Insight into its Phytochemistry and Bioactivity

Can Kerem ÇEVİK [1], Kevser TABAN AKÇA [1], İpek SUNTAR [1]*

[1] Department of Pharmacognosy, Faculty of Pharmacy, Gazi University, Etiler 06330 Ankara, Türkiye.
* Corresponding Author. E-mail: ipesin@gazi.edu.tr (I.S.); Tel. + 90 312 202 31 76.

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ABSTRACT: *Cornus mas* L. (Cornelian cherry) (family Cornaceae) is one of the important medicinal plants with a rich phytochemical profile. It is an ornamental plant with edible fruits possessing therapeutic and nutritional values. The fruits have been used in folk medicine since ancient times. They are red-colored, pear-shaped, oval, and sour taste and are often used in the form of beverages, marmalade, and jams, as well as utilized in the cosmetic industry. Phytochemicals reported for *C. mas* are phenolic acids, flavonoids, organic acids, anthocyanins, tannins, fatty acids, iridoids, and carotenoids. Especially, the fruits are rich in anthocyanins, vitamin C, and phenolic compounds. The extracts and compounds from *C. mas* have been investigated for antimicrobial, cytotoxic, anti-inflammatory, antioxidant, antiatherosclerotic, antihyperlipidemic, antidiabetic, anti-colitis, neuroprotective, hepatoprotective, cardioprotective, and nephroprotective activities. The objective of the present review is to summarize the recent studies on the phytoconstituents of *C. mas* and their biological effects.

KEYWORDS: *Cornus mas*; Cornaceae; phytochemistry; biological activity; traditional medicine; natural products

1. INTRODUCTION

Cornus mas L. is a shrub or small tree and belongs to the Cornaceae family. It can grow up to 7-8 meters. The trunk diameter is 25-45 cm. Leaves are lanceolate-broadly elliptical (3-10 cm), with an opposite arrangement and short petiolate. The inflorescence is umbrella-shaped, 1.5-2.5 cm tall and 15-20 flowered. Flowers are pale yellow to greenish and flower rings are in 4-pieces, usually hermaphrodite and the ovary is 2-loculed. It differs from other species of the *Cornus* genus with the feature of opening flower buds before leaf buds. It has oval, pear-shaped, stone fruits ripening in late summer and early autumn. Drupe is ellipse-cylinder shaped, sour tasty, initially yellow then red. These fruits are used in the food and cosmetics industry. The plant grows in broad-leaved forests, and shrubs at an altitudes of 20-1500 m [1].

In the literature, phenolic acids, flavonoids, organic acids, anthocyanins, tannins, fatty acids, iridoids, and carotenoids were reported in *C. mas* various parts. The fruits of this plant are frequently consumed as food (jam, marmalade, syrup, jelly, compote, fruit pulp, must, fresh fruit) since ancient times. In terms of its bioactivity, the plant had antimicrobial, cytotoxic, anti-inflammatory, antioxidant, antiatherosclerotic, antihyperlipidemic, antidiabetic, anti-colitis, neuroprotective, hepatoprotective, cardioprotective, and nephroprotective activities. Its phytochemical composition and biological activities are summarized in Figure 1. *C. mas* is an important plant to be investigated and used as an active agent for the treatment of many diseases evident with scientific verification.

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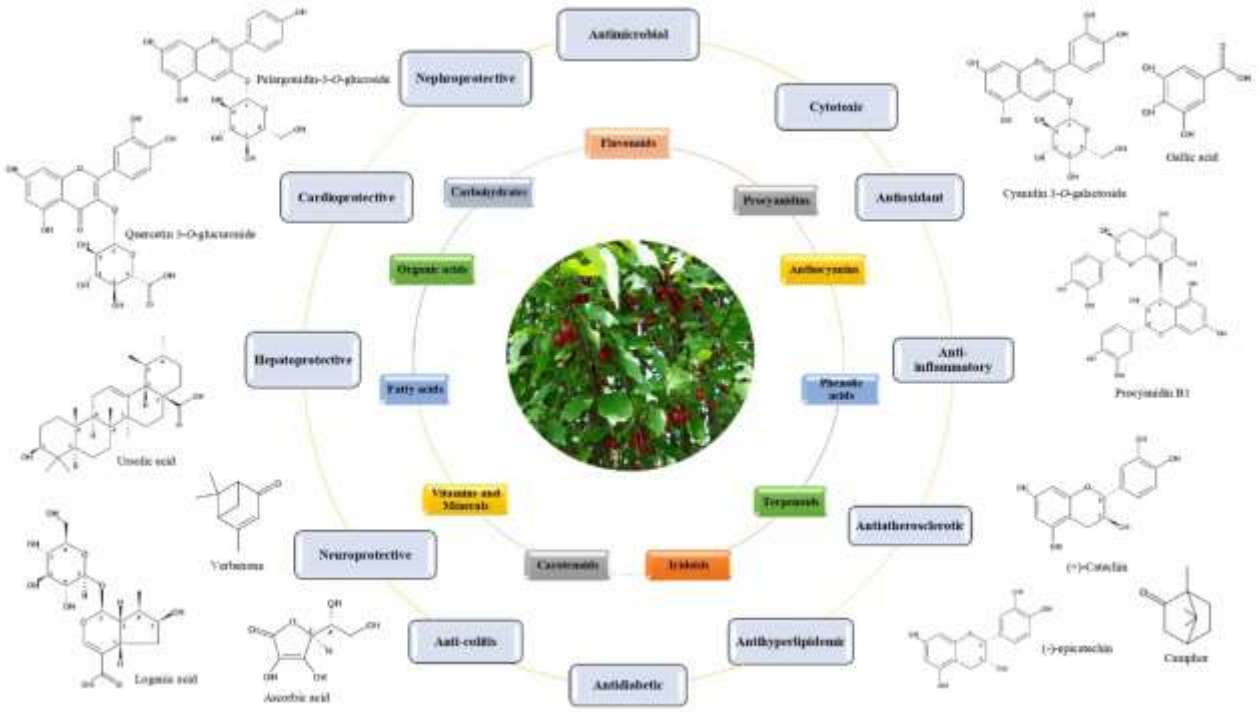
Figure 1. Phytochemical composition and biological activities of *C.mas*



In this study, electronic databases such as Science Direct, Scopus, and PubMed were used to compile the literature. Phytochemical, *in vitro* and *in vivo* studies with English full texts were selected for this review. Phytochemicals reported from the fruits, flowers, and leaves of *C. mas* are summarized in detail. Presented herein is a comprehensive summary in various approaches to *C. mas*.

2. PHYTOCHEMICAL STUDIES ON *CORNUS MAS* L.

In the literature, phytochemicals reported from *C. mas* flowers, fruits and leaves are flavonoids, procyanidins, anthocyanins, phenolic acids, monoterpenes, iridoids, triterpenes, carotenoids, vitamins, fatty acids, organic acids, carbohydrates, and minerals. Especially, the fruits are rich in anthocyanins, vitamin C, and phenolic compounds. Anthocyanins and ascorbic acid are the major compounds in the fruits. The leaves contain higher number of phenolic compounds than fruits; however, anthocyanin has not been reported in the leaves [2]. The flowers are rich in phenolic compounds, flavonoids, and terpenes. Phytochemicals reported for *C. mas* flowers, fruits, and leaves are summarized in Table 1.

Table 1. Phytochemicals reported for *C. mas*

Phytochemical groups	Compound (Plant parts)	References
Anthocyanins	Pelargonidin-3-*O*-galactoside (Fr.)	[8, 11-15]
	Peonidin-3-*O*-glucoside (Fr.)	[5]
	Cyanidin-3-*O*-galactoside (Ideain) (Fr.)	[5, 8, 11-15]
	Pelargonidin-3-*O*-rutinoside (Fr.)	[14]
	Cyanidin-3-*O*-rutinoside (Antirrhinin) (Fr.)	[16]
	Cyanidin-3-*O*-robinobioside (Fr.)	[8, 13]
	Delphinidin-3-*O*-galactoside (Fr.)	
	Pelargonidin-3-*O*-robinobioside (Fr.)	
	Pelargonidin-3-*O*-glucoside (Callistephin) (Fr.)	[14, 16]
	Cyanidin-3-*O*-glucoside (Chrysanthemin) (Fr.)	[16, 17]
Carbohydrates	Fructose (Fr.)	[29, 32]
	Glucose (Fr.)	
	Sucrose (Fr.)	[32]

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Carotenoids	(13Z, 13′Z)-Lutein (Fr.)	[26]
	(9′Z)-Neoxhantin (Fr.)	
	(9Z, 9′Z)-Lutein (Fr.)	
	all-*E*-Neoxhantin (Fr.)	
	Lutein (Fr.)	
	Lutein-5,6-epoxide (Fr.)	
	Luteoxhantin (Fr.)	
	β- Carotene-5,6-monoxide (Fr.)	
	β-Carotene (Fr.)	
	β-Cryptoxhantin (Fr.)	
Fatty acids	2,4-Heptadienoic acid (Fr., L.)	[22]
	Linoleic acid (Fr., L.)	
	Oleic acid (Fr., L.)	
	Palmitic acid (Fr., L.)	
	Palmitoleic acid (Fr., L.)	
	Stearic acid (Fr., L.)	
	α –Linoleic acid (Fr., L.)	
Flavonoids	Luteolin-3-*O*-glucoside (L.)	[2]
	Isorhamnetin-7-*O*-rhamnoside (L.)	[3]
	Kaempferol-3-*O*-glucuronide (L.)	
	Quercetin-3-*O*-galactosyl-7-*O*-rhamnoside (L.)	
	Quercetin (Fr.)	[4]
	Quercetin-3-*O*-robinobioside (Fr.)	[5]
	4-acetoxy-5,2',4',6'-β-pentahydroxy-3-methoxychalcone (Fr.)	[7]
	7,3'-dihydroxy-5,4'-dimethoxyflavanone (Fr.)	
	Aromadendrin (Fr.)	
	Kaempferol-3-*O*-glucoside (Astragalin) (Fr., L.)	[2, 5]
	Naringenin-7-*O*-methyl ether (Sakuranetin) (Fr.)	[7]
	Myricetin (Fr.)	[4, 7]
	Aromadendrin-7-*O*-glucoside (Fr.)	[14]
	Quercetin-3-*O*-galactoside (Hyperoside) (Fr., L.)	[2, 3, 5, 6]
	Quercetin-3-*O*-rhamnoside (Quercitrin) (Fr.)	[5, 14]
	Quercetin-3-*O*-xyloside (Fr.)	
	Quercetin-3-*O*-glucoside (Isoquercetin) (Fr., L.)	[2, 5, 14]
	Kaempferol-3-*O*-galactoside (fr.)	[8, 14]
	Quercetin-3-*O*-glucuronide (Miquelianin) (Fr., L.)	[3, 8, 14]
	Quercetin-3-*O*-rutinoside (Rutin) (Fl., Fr., L.)	[4, 5, 7, 9, 14]
Iridoids	Loganin (Fl.)	[21]
	Sweoside (Fr.)	
	Secologanin (L.)	[25]
	Cornuside (Fr.)	[8, 11, 15, 21]
	Loganic acid (Fl., Fr.)	
Monoterpenes	1,8-Cineol (Fl.)	[24]
	Borneol (Fl.)	
	Camphor (Fl.)	
	Carvacrol (Fl.)	
	Carvon (Fl.)	
	Verbenone (Fl.)	
	α-Terpineol (Fl.)	
	β-Thujene (Fl.)	
	Limonene (Fl.)	[20, 24]
Organic acids	Fumaric acid (Fr., L.)	[22]
	Isocitric acid (Fr.)	
	Malonic acid (Fr., L.)	
	Tartaric acid (Fr.)	[5, 20]
	Oxalic acid (Fr., L.)	[20, 22]
	Succinic acid (Fr., L.)	
	Citric acid (Fr., L.)	[5, 20, 22, 29]

	Malic acid (Fr., L.)	
Phenolic acids	5-*O*-caffeoylquinic acid (Fr.)	[3, 8]
	Salicylic acid (Fr., L.)	[22]
	Vanillic acid (Fr., L.)	
	Quinic acid (Fr.)	[5, 20]
	Shikimic acid (Fr.)	
	Coumaric acid (Fr., L.)	[3, 19, 20]
	Ferulic acid (Fr., L.)	[20, 22]
	Caffeic acid (Fr., L.)	[3, 20, 23]
	Ellagic acid (Fl., Fr.)	[9, 18, 20]
	Gallic acid (Fl., Fr., L.)	[9, 20, 21]
	3-*O*-caffeoylquinic acid (Chlorogenic acid) (Fr.)	[5, 8, 20, 21]
Procyanidins	Catechin (Fr., L.)	[2, 3]
	Epicatechin (Fr., L.)	
	Procyanidin B1 (Fr.)	[5]
	Procyanidin B2 (Fr.)	[2, 5]
Triterpenes	Ursolic acid (Fl., Fr.,)	[9, 12]
Vitamins	Ascorbic acid (Fr.)	[27-30, 52]
	Biotin (Fr.)	[31]
	Riboflavin (Fr.)	
	α-Tocopherol (Fr.)	

*Fl.: Flowers; Fr.: Fruits; L.: Leaves

Flavonol glycosides are prominent among flavonoids and mostly *C. mas* flavonol glycosides include quercetin or kaempferol as the aglycone. Quercetin 3-*O*-glucuronide, kaempferol 3-*O*-galactoside in fruit and quercetin 3-*O*-glucuronide in the leaf are the major flavonoid components. Apart from these, other flavonoid compounds that have been reported for *C. mas* are quercetin-3-*O*-glucoside, quercetin-3-*O*-xyloside, quercetin-3-*O*-rhamnoside, quercetin-3-*O*-rutinoside, quercetin-3-*O*-galactosyl-7-*O*-rhamnoside, quercetin-3-*O*-robinobioside, kaempferol-3-*O*-glucoside, kaempferol-3-*O*-galactoside, kaempferol-3-*O*-glucuronide, isorhamnetin-7-*O*-rhamnoside, myricetin, aromadendrin, aromadendrin-7-*O*-glucoside, naringenin-7-*O*-methyl ether, luteolin-3-*O*-glucoside, 4-acetoxy-5,2',4',6'-β-pentahydroxy-3-methoxychalcone and 7,3'-dihydroxy-5,4'-dimethoxyflavanone [2-9]. Among the proanthocyanidins, (+)-catechin, (-)-epicatechin, procyanidin B1, and procyanidin B2 were isolated from *C. mas* fruit and leaf [2, 3, 5]. It has been reported that the total anthocyanin content in the fruits of *C. mas* and other *Cornus* species is higher than in other fruits and vegetables [10]. Cyanidin 3-*O*-galactoside and pelargonidin 3-*O*-galactoside are the major among the isolated anthocyanins. Pelargonidin-3-*O*-glucoside, pelargonidin-3-*O*-robinobioside, pelargonidin-3-*O*-rutinoside, cyanidin-3-*O*-glucoside, cyanidin-3-*O*-robinobioside, cyanidin-3-*O*-rutinoside, peonidin-3-*O*-glucoside, delphinidin-3-*O*-galactoside are other isolated compounds [5, 8, 11-17]. Gallic acid, ellagic acid, shikimic acid, vanillic acid, chlorogenic acid, salicylic acid, quinic acid, 3-*O*-caffeoylquinic acid, 5-*O*-caffeoylquinic acid, coumaric acid, caffeic acid, and ferulic acid were reported to be isolated from *C. mas* [3, 5, 8, 9, 18-23]. Monoterpenoids were identified as the main components in the essential oil of flowers. Camphor, borneol, verbenone, carvone, carvacrol, β-thujene, α-terpineol, 1,8-cineol and limonene were isolated from *C. mas* flowers. Camphor and verbenone were the most common compounds [20, 24]. Among iridoids, loganic acid was the major iridoid compound. In addition, loganin, cornuside, sweoside, secologanin were isolated [8, 11, 15, 21, 25]. On the other hand, only ursolic acid was reported as the triterpenoid compound in *C. mas* flowers and fruits [9, 12]. Carotenoids exist in fresh fruits of *C. mas.* Reported caretonoids were β-carotene, β-carotene-5,6-monoxide, β-cryptoxhantin, lutein, lutein-5,6-epoxide, luteoxhantin, (9*Z*, 9′*Z*)-lutein, (13*Z*, 13′*Z*)-lutein, all-E-neoxhantin and (9'Z)-neoxhantin [26]. Vitamin C (ascorbic acid) level was reported to be high in *C. mas* fruits. Other reported vitamins were biotin, α-tocopherol, and riboflavin [27-31]. According to the literature, linoleic acid, oleic acid, stearic acid, palmitic acid, palmitoleic acid, α-linoleic acid, 2,4-heptadienoic acid were detected in *C. mas* fruits and leaves. Linoleic acid and oleic acid were present in the highest amounts in fruits, while 2,4-heptadienoic acid and palmitic acid were in the highest level in leaves [22]. Organic acids namely tartaric acid, fumaric acid, citric acid, malic acid, oxalic acid, succinic acid, malonic acid, and isocitric acid were isolated from *C. mas* [5, 20, 22, 29]. Glucose, fructose, and sucrose were also reported for *C. mas* fruits [29, 32]. *C. mas* fruits were reported to contain many minerals including calcium, sodium, zinc, copper, magnesium, etc.

3. ETHNOMEDICAL USE OF *CORNUS MAS* L.

Fruits, flowers, and leaves of *Cornus* species have been traditionally used against sore throat, measles, chickenpox, anemia, kidney and liver ailments, and digestive system disorders in many parts of the world [33-35].

The homeland of the cornelian cherry is Türkiye, Caucasus, and Europe. It not only grows wild in the forests of Northern Anatolia but also is cultured in gardens in many regions of Anatolia for its fruit [16]. Ripe fruits are eaten or consumed as soup. The paste prepared from fruits is called "kiren sour, zirta or zirte" [36, 37]. In the folk medicine worldwide, fruits, leaves, and seeds are used directly or in processed form (extracts, fermented products, etc.) to treat colds, fever, heatstroke, cough, bronchitis, diabetes, urinary tract infections and inflammation, diarrhea, abdominal pain, ulcer, and wounds [9, 31, 34, 38-67]. Decoction prepared from the fruits is used in the treatment of colds and diarrhea; the seeds are swallowed in the morning before breakfast against diabetes; infusion prepared from the leaves is used as a regulator of blood sugar and an anti-diarrheal [39, 64]. It has been reported that the soup prepared with flour after the boiling of fruits and seeds is used against bronchitis and colds, and the syrup prepared by boiling with sugar is used against sunstroke by drinking [38]. An infusion prepared from the trunk and branch barks is used as anthelmintic, antipyretic, and anti-diarrheal due to the tannin-type compounds [68]. Table 2 summarizes the ethnomedical use of *C. mas* in the world.

Table 2. Ethnomedical use of *C. mas*

Country	Use	Plant parts	Preparation	References
Albania	Asthmatic problems	Fr.	Fermented in raki	[44]
	Fever	Fr.	Fermented in vinegar	[44]
	Defecation problems and inflammation	Fr.	Decoction	[44]
	Antirheumatic	Fr.	Fermented in raki	[50]
	Kidney stones and rheumatic diseases	Fr.	-	[45]
Armenia	Cholera	Fr.	-	[46]
Azerbaijan	Sore throat, defecation problems, measles, rubella, anemia, rickets	Fr., Fl., L.	Galenic use	[34]
	Fever	B.	The decoction of the dried leaves is mixed with *Angelica* sp.	[47]
	Diarrhea	Fr.	Infusion	[47]
Bosnia and Herzegovina	Diarrhea, menstrual problems, skin disorders	Fr., B.	-	[48]
China	Diabetes and renal dysfunction	Fr.	-	[49]
Greece	Gout, anemia, skin ailments, joint pain, metabolism disorders	Fr.	Galenic usage	[51]
	Gastrointestinal problems, tuberculosis and menstrual problems	Fr., L., B.	-	
Iranian	Urinary inflammation	Fr., L.	-	[52]
	Fever, diarrhea, malaria, intestinal diseases, kidney stone and infections, cancer, sunstroke	Fr.	-	[52]
Italy	Dermocosmetics	Fr.	-	[53]
	Dyspepsia and colitis	Fr.	-	[54]
	Loss of appetite	Fr.	Fresh and ripe fruit is fermented in vinegar or liquor	[55, 56]
Kosovo	Rheumatism, anemia, blood circulation disorders	Fr.	Decoction	[57]
	Diabetes	Fr.	Fruit juice	
Macedonia	Diarrhea and loss of appetite	Fr.	Compote	[45]

Romania	Diarrhea	Fr.	Infusion/decoction	[58]
	Fever, dysentery	Fr., L., B.	Infusion/decoction	[58]
	Cardiac problems	L.	-	[59]
Serbia	Diarrhea	Fr.	Fresh or dried fruit infusion	[9, 60]
	Laxative	Fr.	Raw fruit	[60]
	Diarrhea, digestive system problems, anemia, immune system booster	Fr., Fl.	Infusion, tisane	[61]
Slovakia	Fever	Fr.	-	[62]
	Defecation problem and inflammation	Fr.	-	
Turkey	Common cold	Fr., L.	Infusion	[41]
	Urinary inflammation			
	Common cold, bronchitis	Fr.	Pitted fruits are boiled and turned into a soup with flour	[38]
	Digestive system problems	Fr.	-	[63]
	Diarrhea	Fr.	Fresh fruit by eating / infusion	[38, 39, 63-65]
	Diabetes	Fr., L.	Decoction	[38]
		S.	With honey before breakfast mixed and swallowed	[39]
	Bronchitis and cough	Fr.	Decoction	[38, 39]
	Sunstroke	Fr.	Fruits with sugar mixed and eaten	[38]
	Wound healing	Fr.	Decoction	[40]
Ukraine	Diabetes	Fr.	Juice	[66]
United States	Cystitis, sweating and menstrual bleeding	Fr.	-	[67]

B.: Barks; Fl.: Flowers; Fr.: Fruits; L.: Leaves

4. BIOACTIVITY STUDIES ON *CORNUS MAS* L.

Numerous pharmacological research has been conducted on the utilization of *C. mas* in folk medicine. Some of these studies resulted in the purification of active compounds, while some of them were at the level of the confirmation of conventional use of the plant or its extracts. Activity studies on *C. mas* were summarized in Table 3.

Table 3. Activity studies on *C. mas*

Activity	Clinical trial/*in vivo*/*in vitro*	Plant Parts	Extract Type	References
Antimicrobial	*in vitro*	Fr.	Methanol: acetone: water: formic acid (30: 42: 27.5: 0.5)	[2]
	in vitro	L.	Methanol: acetone: water: formic acid (30: 42: 27.5: 0.5)	
	in vitro	Fr.	*n*-Hexane	[35]
	in vitro	-	80% Ethanol	[69]
	in vitro	Fr.	Methanol	[70]
	in vitro	Fr.	Ethanol	
	in vitro	L.	Methanol	
	in vitro	L.	Ethanol	
	in vitro	Pl.	Methanol and ethanol	

	in vitro	Sd.	Methanol and ethanol	
	in vitro	Fr.	Ethanol	[71]
	in vitro	Fr.	Methanol	[72]
	in vitro	Fr.	Water	
	in vitro	Fr.	Juice	[73]
	in vitro	Fr.	PBS	[74]
	in vitro	Fr.	PBS: Water	
	in vitro	Fr.	Water	
	in vitro	Fr.	Methanol	
Antioxidant	*in vitro*	Fr.	Acetone: methanol: water: formic acid (40: 40: 20: 0.1)	[16]
	in vitro	Fr.	Acetone	[23]
	in vitro	Fr.	Methanol	[75]
	in vitro	Fr.	50% Methanol	[76]
	in vitro	L.	50% Methanol	
	in vitro	L.	80% Methanol	[77]
	in vivo	L.	80% Methanol	
	in vitro	Fr.	-	[78]
	in vitro	Fr.	Methanol	[79]
	in vitro	Fr.	40% Ethanol	[80]
	in vitro	Fr.	Water	
	in vitro	Fr.	Juice	[81]
Anti-inflammatory	*in vivo*	Fr.	Acetone	[23]
	in vitro	Fr.	Methanol	[75]
	in vivo	-	Water	[82]
Anti-platelet	*in vivo*	Fr.	Aqueous methanol	[18]
Anti-glaucoma	*in vivo*	Fr.	Juice	[8]
Anti-atherosclerotic	*in vivo*	Fr.	-	[90]
	in vivo	Fr.	Anthocyanin fraction and loganic acid (isolated compound)	[91]
Antidiabetic	*in vivo*	Fr.	-	[83]
	in vivo	Fr.	-	[87]
	in vivo	Fr.	Ethanol	[88]
	in vivo	Fr.	-	[89]
	in vivo	Fr.	-	[85]
	in vivo	Fr.	Ethanol	[86]
	Clinical trial	Fr.	70% Ethanol	[84]
Aldose reductase inhibitor	*in vitro*	L.	Water	[92]
Cardioprotective	*in vivo*	Fr.	Aqueous-alcoholic	[93]
Hepatoprotective	*in vivo*	Fr.	Methanol: water (7: 3)	[94]
	Clinical trial	Fr.	80% Ethanol	[95]
Nephroprotective	*in vitro*	Fr.	Water	[96]
	in vivo	Fr.	Methanol	[97]
Neuroprotective	*in vivo*	Fr.	-	[98]
	in vivo	Fr.	-	[99]
Radioprotective	*in vitro*	L.	Methanol	[100]
Protective effect on reproductive system	*in vivo*	Fr.	Methanol	[101]
Cytotoxic	*in vitro*	Fr.	Aqueous-alcoholic	[102]
	in vitro	L.	Water	[103]
	in vitro	Fl.	Methanol	[104]
	in vitro	L.	Methanol	
Anti-colitis	*in vivo*	Fr.	80% Methanol	[105]

Fl.: Flowers; Fr.: Fruits; L.: Leaves; Pl.: Peels; Sd.: Seeds

4.1. Antimicrobial effect

In a study conducted in Azerbaijan, the antimicrobial activity of fatty acids obtained from *C. mas* fruits was investigated. The collected fruits were dried, powdered, then extracted with *n*-hexane. Antimicrobial activity was evaluated by agar diffusion test against *Staphylococcus aureus* and *Escherichia coli*. The oil obtained from *C. mas* fruits was found to have a significant antimicrobial effect against *Staphylococcus aureus* and *Escherichia coli* [35]. In another study by Dulger and Gonuz the antimicrobial activity of 80% ethanol extract of *C. mas* was assessed by using agar disk diffusion method and the extract showed an inhibitory effect against *Pseudomonas aeruginosa, Proteus vulgaris, Staphylococcus aureus,* and *Micrococcus luteus* [69]. Antimicrobial effects of methanol and ethanol extracts of *C. mas* fruit, seed, leaf, and peel were tested against *Streptococcus pyogenes, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Candida albicans, Aspergillus fumigatus,* and *Trichophyton mentagrophytes*. Sabouraud glucose agar was used for fungi. Agar diffusion test was used for antibacterial, and antifungal activities. *C. mas* extracts (20 µL) were applied in 3 different concentrations (10 $mgmL^{-1}$, 1 $mgmL^{-1,}$ and 0.1 $mgmL^{-1}$). Ethanol and methanol extracts of the seeds and leaves with the ethanol extract of barks and the methanol extract of fruits showed antibacterial effects against *S. aureus.* The ethanol extract of seeds, leaves, and barks with both methanol and ethanol extracts of fruits were found to be effective against *P. aeruginosa.* The leaf and seed ethanol extracts and the fruit methanol and ethanol extracts were active against *E. coli*; the leaf and seed ethanol and methanol extracts were effective against *C. albicans*; the seed methanol extract was found to be effective against *A. fumigatus*. On the other hand, all extracts showed resistance to *S. pyogenes* and *T. mentagrophytes* [70]. Turker et al. investigated the antibacterial and antitumor effects of 8 different plants including *C. mas* fruits. Antibacterial effects of cold and hot extracts of dried and fresh fruits were investigated by the disc diffusion method. Cold or hot ethanol extracts of fresh fruits of *C. mas* were found to have moderate antibacterial activity against *S. epidermidis, S. aureus, S. pyogenes,* and *E. coli.* Also, cold and hot aqueous extracts of *C. mas* fresh fruits showed a low inhibitory effect against *E. coli* [71].

In another study, *C. mas* fruits and leaves were extracted with methanol: acetone: water: formic acid (30:42:27.5:0.5) mixture. The antimicrobial effect of *C. mas* fruit and leaf extracts was investigated against Gram-positive bacteria (*Bacillus cereus, Clostridium perfringens, Listeria monocytogenes, Sarcina lutea, Staphylococcus aureus,* and *Micrococcus flavus*); Gram-negative bacteria (*Pseudomonas aeruginosa, Klebsiella pneumoniae, Shigella sonnei, Salmonella enteritidis, Proteus vulgaris,* and *Escherichia coli*) and *Candida albicans* fungi by comparing the effects with the positive control (tetracycline) and negative control (methanol). After incubation of bacteria on agar and transfer to petri dishes, antimicrobial activities of extracts were evaluated by measuring the inhibition zone. *Clostridium perfringers, Sarcina lutea, Listeria monocytogenes, Shigella sonnei, Salmonella enteritidis,* and *Proteus vulgaris* were found to be sensitive to the extracts. However, the leaf extract displayed a higher antimicrobial effect than the fruit extract. The antimicrobial effects of these extracts were attributed to high total phenol content [2]. Antimicrobial effects of methanol and aqueous extracts of *C. mas* fruits were evaluated. Antimicrobial activities of fruit extracts against 93 clinical isolates of human pathogenic strains (*Escherichia coli, Enterobacter aerogenes, Pseudomonas aeruginosa, Staphylococcus aureus,* and *Proteus mirabilis*) and 5 fungal strains (*Candida albicans, C. krusei, C. parapisilosis, C. glabrata,* and *C. tropicalis*) were evaluated by disc diffusion method. It was observed that methanol and aqueous extracts of fruits had an antibacterial effect against Gram-positive and negative bacteria. *C. mas* fruits' methanol extracts were active against *P. aeroginosa, E. coli, S. aureus,* and *C. albicans*; and the aqueous extract was active against *S. aureus* and *E. coli* [72]. Krisch et al. investigated the antibacterial activity of the extracts and juices of some cultivated and wild fruits belonging to various families by using disc diffusion method. Microdilution plate assays were used to evaluate *in vitro* antibacterial activities. Considerable activity against *Bacillus subtilis, Bacillus cereus, Escherichia coli,* and *Serratia marcescens* was detected for *C. mas* extracts and juices [73]. In another study, phosphate-buffered saline (PBS), PBS: water, water and methanol extracts of *C. mas* fruits were evaluated for their antibacterial potential. As a result, all tested extracts showed potent activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa* [74].

4.2. Antioxidant effect

The activity of methanol extract of *C. mas* on iron chloride catalyzed liposome oxidation was evaluated. As positive control, tert-butylhydroquinone (TBHQ), butyl hydroxyanisole (BHA), butyl hydroxytoluene (BHT), and tocopherol were used. The antioxidant effect of positive control groups was 83.2% for TBHQ; 79.7% for BHT; 82.1% for BHA and 10.2% for vitamin E. The antioxidant activities of

anthocyanins isolated from *C. mas* (delphinidin-3-*O*-galactoside, cyanidin-3-*O*-galactoside and pelargonidin-3-*O*-galactoside) were 70.2%, 60.1% and 40.3%, respectively [75]. Tural and Koca examined the physical, chemical, and antioxidant effects of *C. mas* fruits. For this purpose, *C. mas* fruits were extracted with acetone: methanol: water: formic acid (40: 40: 20: 0.1) mixture. Antioxidant activity was measured by using iron reduction (FRAP) and 2,2-diphenyl-1-picrilhydrazil (DPPH) free radical scavenging assay. It was determined that *C. mas* fruit extract showed antioxidant effect with the value of 53.92±20.12 µgmL^{-1} in FRAP experiment and with the EC_{50} value of 1.8-10.9 µgmL^{-1} in DPPH experiment [16].

Serteser et al. studied the antioxidant activities of some plants growing wild in Türkiye. For this purpose, *C. mas* leaves and fruits were extracted with 50% aqueous methanol. The antioxidant effect of the extract was evaluated by using DPPH, hydrogen peroxide radical scavenging assay and iron chelation methods. While DPPH free radical scavenging effect of the leaf extract was higher than that of the fruit extract, the fruit extract was more active in iron chelation. The highest hydrogen peroxide inhibition activity was determined for *C. mas* extracts compared to the other plants used in the study [76].

Celep et al. evaluated *in vitro* and *in vivo* antioxidant effect potentials of *C. mas* leaves. The antioxidant activity of 80% methanol extract of *C. mas* leaves and *n*-hexane, chloroform, ethyl acetate, *n*-butanol, and aqueous sub-extracts prepared from this extract were evaluated using *in vivo* and *in vitro* methods. *In vitro* antioxidant effect, DPPH and superoxide radical scavenging activity, FRAP, and copper ion reduction (CUPRAC) antioxidant capacity, iron ions chelation activity, total antioxidant capacity, effect on β-carotene/linoleic acid system and Trolox equivalent antioxidant capacity were evaluated. In *in vivo* antioxidant studies, 18 experimental male rats were divided into 3 groups; each group consisted of 6 animals; i: control group; ii: 50 mgkg^{-1} silymarin-treated reference group; iii: experimental group *C. mas* leaf extract-treated group (500 mgkg^{-1}). Test samples were administered to the animals for 21 days and blood samples were taken on the 22nd day. In the second stage, the rats with carbon tetrachloride-induced experimental model were divided into 6 groups; i: control group (0.5% CMC, 1 mgkg^{-1}, olive oil p.o.); ii: group receiving carbon tetrachloride (0.5% CMC, carbon tetrachloride on days 2 and 3: olive oil (1:1), 2 mgkg^{-1}); iii, iv, v: test groups (*C. mas* methanol leaf extract 100, 200 and 500 mgkg^{-1} respectively, carbon tetrachloride on days 2 and 3: olive oil (1:1), 2 mgkg^{-1}); vi: reference group (50 mgkg^{-1} silymarin, carbon tetrachloride on days 2 and 3: olive oil (1:1), 2 mgkg^{-1}). The samples were applied to the animals for 5 days and the experiment was terminated on the 6th day. According to the outcome of the *in vitro* experiments, it was revealed that the extract displayed significant DPPH radical scavenging activity but exerted a lower superoxide scavenging effect. The iron reduction capacity and β-carotene bleaching power of the extract were higher than those of the reference group. In the CUPRAC test, the extract showed good metal reduction activity. Antioxidant studies in healthy rats showed no change in superoxide dismutase, catalase, and glutathione peroxidase activities and lipid peroxidation levels, but exerted enhancement in the total antioxidant capacity of liver homogenates. Improvement in the antioxidant enzyme activity, reduction in lipid peroxidation levels, and increase in the total antioxidant capacity of both blood and liver homogenates were detected in *C. mas* extract treated rats [77].

Sengul et al. investigated the chemical content and antioxidant capacity of *C. mas* against BHA reference material using β-carotene bleaching method. Total antioxidant activity of *C. mas* genotypes was found to be between 84.68% and 94.17% ($p<0.01$). Phenolic compounds are thought to be responsible for antioxidant activity [78]. To evaluate *in vitro* antioxidant effect of *C. mas*, the fresh fruits were homogenized and extracted with acetone for one hour at room temperature. FRAP and 2,2'-azinobis-3-ethyl-benzthiazino-6-sulfonic acid (ABTS) tests were used. In both experiments, it was reported that *C. mas* fresh fruits showed antioxidant activity [23]. Antioxidant capacity Romanian *C. mas fruits* was evaluated by DPPH assay. According to the results, the value was detected as 1.91 ± 0.25 mmol trolox/100 g [79]. Szczepaniak et al. investigated seven genotypes of *C. mas* fruits from Poland by DPPH and ABTS assays. Aqueous and 40% ethanol extracts of the fruits were prepared. The results showed that inhibition values were between 0.392 ± 0.023 and 6.591 ± 0.090 for ABTS (mmol TE/100 g dried weight) and were 0.8546 ± 0.1849 and 10.3980 ± 0.4282 for DPPH (mmol TE/100 g dw) for all genotypes [80]. Strong antioxidant activity was detected for lyophilized *C. mas* juice extract with the IC_{50} value of 0.067 ± 0.001% (DPPH) [81].

4.3. Anti-inflammatory effect

The bioactivity, characterization, and number of anthocyanins obtained from *Cornus* species were investigated. *C. mas* fresh fruits were homogenized, extracted with methanol containing 1% hydrochloric acid and centrifuged. The anthocyanins in the extract were determined and quantified by High Pressure

Liquid Chromatography (HPLC). The anthocyanins (cyanidin-3-*O*-galactoside, delphinidin-3-*O*-galactoside, and pelargonidin-3-*O*-galactoside) isolated from the extract were evaluated for their inhibitory effects on cyclooxygenase (COX)-1 and COX-2 enzymes. Moderate inhibitory effects of these compounds have been reported [75].

Potential activity of *C. mas* fruits on acute inflammation was investigated using *in vivo* methods. *C. mas* fresh fruits were homogenized and extracted with acetone for one hour at room temperature and concentrated. The anti-inflammatory activity of the extract was evaluated by measuring cytokine levels in Wistar rats with carrageenan-induced hind paw edema. Rats were randomly divided into 4 groups with 8 animals in each group: i: positive control group; ii: indomethacin-treated reference group (5 $mgkg^{-1}$); iii: *C. mas* extract with a total phenol content of 15 $mgkg^{-1}$; iv: *C. mas* extract with a total phenol content of 30 $mgkg^{-1}$. At the end of the experiment, it was determined that *C. mas* extract showed strong *in vitro* antioxidant activity and increased IL-10 production by suppressing the production of interleukin (IL)-1β and IL-13 significantly. Histopathological examinations revealed that *C. mas* extract with 15 $mgkg^{-1}$ total phenol content alleviated acute inflammation and *C. mas* extract with 30 $mgkg^{-1}$ total phenol content prevented inflammatory cells from migrating to the inflammation site [23]. Another study was conducted to evaluate the comparative effects of silver (AgNPs-CM) and gold (AuNPs-CM) nanoparticles functionalized with polyphenols from *C. mas* extract on *in vivo* experimental inflammation. Oxidative stress parameters, pro and anti-inflammatory cytokine levels and apoptosis assessment were used to determine the regulatory effects of AgNPs-CM and AuNPs-CM on inflammation. 0.3 mg body weight (bw) AgNPs-CM and AuNPs-CM administration for 4 consecutive days before carrageenan injection decreased IL-1α, IL-1β, IL-6 and monocyte chemoattractant protein-1 [82].

4.4. Anti-platelet effect

In a study, the activities of *C. mas* aqueous methanol extract on blood glucose level, hematological parameters and lipid profile in male rats were investigated. In the study, 40 male rats, 8 animals in each group were divided into i: normal group (standard diet); ii: placebo control group (saline, 21 days); iii, iv, v: experimental groups (*C. mas* extract, 3 weeks, p.o., at doses of 50, 200 and 400 $mgkg^{-1}$, respectively). At the end of the experiment, a remarkable decrease was found in platelet distribution with compared to the control group ($p=0.001$) [18].

4.5. Anti-glaucoma activity

Szumny et al. investigated the anti-glaucoma effect of polyphenol fraction of *C. mas* fruit and loganic acid, an iridoid compound. For this purpose, the seeds of *C. mas* fruits were removed and fruit juice was obtained by depectinization. The fruit juice was fractionated and isolated using AmberliteTM XAD-16 resin column. To evaluate the effect of polyphenol fraction and loganic acid on intraocular pressure and blood flow in iris, 14 New Zealand rabbits (7 male and 7 female) aged between 12-15 months were used. Artificial tear solution (0.15% sodium hyaluronate) containing 0.7% loganic acid or polyphenolic fraction was prepared. In the right eye of each animal (study group), eye drops containing 0.7% loganic acid or polyphenolic fraction; in the left eye, placebo (control group) was administered intraconjunctivally at a volume of 50 µL each. Intraocular pressure was then measured in both eyes before and at 1, 2, 3, 4, and 5 hours after administration. The results showed that loganic acid reduced intraocular pressure by approximately 25% at 3 hours of use [8].

4.6. Antidiabetic, hypolipidemic, and antiatherosclerotic effect

The antidiabetic effect of *C. mas* in rats with alloxan-induced diabetes was compared with glibenclamide. Male Wistar rats with 8 animals in each group were divided into 4 groups, i: control group without diabetes model, ii: diabetes-induced and untreated group; iii: diabetes-induced and glibenclamide (0.6 $mgkg^{-1}$) treated group; and iv: diabetes-induced experimental group treated with *C. mas* fruits (2 $gday^{-1}$). Diabetes was induced by a single dose of 120 $mgkg^{-1}$ intraperitoneal injection of alloxan. The results showed that treatment with *C. mas* fruits decreased blood glucose levels and increased insulin levels compared with the diabetic group without any treatment. The concurrent histological studies on the pancreas showed similar results. According to histological analysis, *C. mas* fruits increased the size of pancreatic islets compared to diabetic groups ($p<0.05$). As a result, *C. mas* fruits have an antidiabetic effect and improve pancreatic damage caused by free radicals in diabetes. The activities of the fruits were attributed to

anthocyanins and other antioxidant compounds [83]. Soltani et al. evaluated the effect of the fruit extract of *C. mas* on the biomarkers of glycemic control in adult type 2 diabetes patients in a randomized double-blind placebo-controlled study. Ethanol (70%) extract was prepared from the fresh fruits of *C. mas* and was standardized to the total anthocyanin content, mixed with tribasic calcium phosphate, then granulated into 500 mg capsules containing 150 mg anthocyanin. The inclusion criteria of the patients were determined according to the American Diabetes Association (ADA) diagnostic criteria. Accordingly, sixty patients (between 18 and 80 years) with type 2 diabetes at least 2 years without diabetic foot ulcer, without renal, liver, or cardiovascular diseases, were included. The patients were randomly divided into two groups and given placebo or extract capsules (2 capsules, 2 times a day) for 6 weeks. Fasting blood glucose, insulin, glycosylated hemoglobin (HbA1c) and TG levels as well as 2-hour postprandial glucose concentration were measured before and after administration and the mean values were compared between the groups. After 6 weeks of administration, a remarkable enhancement in insulin level was observed. *C. mas* was found to reduce serum levels of HbA1c and increase serum insulin levels compared to placebo [84]. Capcarova et al. investigated the activity of *C. mas* fruit on the development of diabetes mellitus symptoms in ZDF rats. *C. mas* was given in two doses (500 and 1000 $mgkg^{-1}$) to rats orally for 10 weeks. According to the results, it was determined that there was a significant decrease in glucose level at the dose of 1000 $mgkg^{-1}$ [85]. Dzydzan et al. investigated the effects of ethanol extracts of red and yellow fruits of *C. mas* in rats with streptozotocin-induced diabetes mellitus. Rats with type 1 diabetes were given the extracts at 20 $mgkg^{-1}$ bw dose orally for 14 days. Cornelian cherry extracts decreased blood glucose and enhanced glucose tolerance. Also, in diabetic rats, yellow fruit extracts increased the level of reduced glutathione and mean cell hemoglobin [86].

In another study, the activity of dietary *C. mas* fruits on serum glucose and insulin and body weight was investigated. For this purpose, *C. mas* fruits were pulverized after drying. For the experiment, 36-month-old male hamsters were divided into 4 groups consisting of 9 animals in each group, i: control group (the group fed basal diet without fruit support); ii, iii, iv: test groups (the groups fed the basal diet with *C. mas* fruits support 5 g per day, 10 g per day and 15g per day, respectively) and the experiment was continued for 20 days. All animals were weighed at the beginning and end of the experiment. At the end of the experiment, 3 animals were randomly selected and killed by the exsanguination method. Blood insulin and glucose levels were measured. It was found that dietary *C. mas* fruits provided a significant decrease in body weight, and this reduction showed a negative correlation with the amount of supplementation. It was suggested that the decrease in body weight could have been caused by the hypoglycemic effects of *C. mas* fruits. Based on serum biochemical analysis, animals were given *C. mas* fruits only once a day and a significant decrease in glucose was detected in these groups. This was related to the increase in insulin levels ($p<0.05$). The response to hypoglycemic effect was not increased by *C. mas* fruit supplementation (two or three times a day) and no notable difference was found between the glucose level of the experimental group and the control group. It was concluded that *C. mas* fruit supplements given in two or three meals a day may reduce weight gain and provide a remarkable hypoglycemic effect [87]. In a similar study, the anti-hyperlipidemic and anti-hyperglycemic effects of *C. mas* fruit ethanol extract were investigated in diabetic rats in comparison to glibenclamide. The rats were divided into 4 groups, i: normal group (2 $mLkg^{-1}$ saline, i.p.); ii: diabetic control group (120 $mgkg^{-1}$ alloxane monohydrate, i.p.); iii: extract group (100 $mgkg^{-1}$ *C. mas* extract, i.p.) and iv: reference group (500 μgkg^{-1} glibenclamide, i.p.). After 72 hours, blood samples were taken under anesthesia and serum glucose, TG and lipoprotein levels were measured. As a result, there were a remarkable decrease in glucose, TG, LDL and Very Low-Density Lipoprotein Cholesterol (VLDL) levels in the *C. mas* extract group compared to the control group ($p<0.001$). The decrease in glucose and LDL levels was similar to the reference group treated with glibenclamide. The decrease in TG and VLDL levels was found to be higher in the experimental group in which *C. mas* extract was applied. When evaluated in terms of HDL levels, it was found that *C. mas* group showed a notable increase similar to glibenclamide [88]. In a study by Asgary et al. the anti-hyperlipidemic and anti-hyperglycemic effect of *C. mas* fruits was evaluated in alloxan-induced diabetes in mice. The rats were divided into 7 groups (n=7): i: non-diabetic control group; ii: diabetic control group; iii: group treated with glibenclamide (0.6 $mgkg^{-1}$ per day; 4 weeks) and iv: group treated with *C. mas* fruits (2 g per day; 4 weeks). Diabetes was induced by a single dose of alloxan (120 $mgkg^{-1}$) injection. After 4 weeks, blood samples were taken from mice (retro-orbital plexus) for 16 hours and serum glucose concentrations, TC, TG, AST, ALT, LDL, and HDL values were measured. In diabetic rats, serum glucose, LDL, TG, AST, ALP and ALT levels were significantly higher and HDL levels were lower than non-diabetic group ($p<0.05$). Application with glibenclamide or *C. mas* fruits offset the above-mentioned

abnormalities. In conclusion, it was found that *C. mas* fruits effectively prevent diabetes development due to alloxan-induced dyslipidemia and hepatic inflammation [89].

A study conducted in Iran; it was aimed to assess the healing effect of *C. mas* in atherosclerosis. 25 male New Zealand rabbits (2 to 2.5 kg) were divided into 5 groups and animals were fed for 60 days by applying different dietary regimens; i: standard diet; ii: standard diet and *C. mas* (1 gkg^{-1} per day); iii. hypercholesterolemic diet; iv: hypercholesterolemic diet and *C. mas* (1 gkg^{-1} per day); v: hypercholesterolemic diet and lovastatin (10 $mgkg^{-1}$ per day). Plasma total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) antioxidant capacity, malondialdehyde (MDA) and fibrinogen levels were measured before and after the experiment. Hypercholesterolemic diet caused a significant increase in TG, LDL, atherogenic index, blood sugar and AST levels ($p<0.05$). There was no notable change in antioxidant capacity, HDL, ALT and MDA levels. A significant decrease in total cholesterol, MDA, fibrinogen, and atherogenic index levels and an increase in antioxidant capacity were observed in rabbits fed *C. mas* with hypercholesterolemic diet compared to the group fed with hypercholesterolemic diet alone ($p<0.05$). At the same time, there was an increase in HDL level and a decrease in blood sugar, TG, AST and ALT levels in this group. In the normal diet group, there was no atherosclerotic change, but in the hypercholesterolemic diet group, fat-loaded macrophage plaque thicknesses on the intima surface of the aortic artery according to Chekanov scale were determined. In the hypercholesterolemic diet and *C. mas* given group, plaque grade was found to be 2. It was concluded that *C. mas* may be beneficial for hypercholesterolemic patients owing to anti-inflammatory and antioxidant effects [90]. In another study, the anti-atherosclerotic effect of *C. mas* was investigated. For this purpose, 40 New Zealand rabbits were divided into 4 groups, each consisting of 10 animals; i: fed on a standard diet; ii: 1% cholesterol-enriched diet; iii: loganic acid (20 $mgkg^{-1}$ per day) isolated from *C. mas* fruits with a hypercholesterolemic diet; iv: anthocyanin fraction (10 $mgkg^{-1}$ per day) obtained from *C. mas* fruits together with hypercholesterolemic diet. The experiment continued for 60 days and blood samples were taken at the end of the experiment. Plasma L-arginine, asymmetric dimethylarginine (ADMA), symmetric dimethylarginine (SDMA), dimethylarginine (DMA) and L-citrulline levels were evaluated using liquid chromatography-mass spectrometry (LC-MS/MS). Dimethylarginine dimethylaminohydrolase (DDAH) activity and redox parameters were analyzed by spectrophotometric method. DDAH1 and DDAH2 isoform expressions were evaluated by Western Blot technique, endothelial nitric oxide synthetase (eNOS) and messenger ribonucleic acid (mRNA) were measured by real-time polymerase chain reaction (PCR). Application of loganic acid and anthocyanin was found to cause an increase in the level of L-arginine and L-arginine/ADMA ratio. Also, ADMA, DMA and L-citrulline levels decreased in both groups; no change in SDMA levels was observed. Anthocyanins significantly increased DDAH activity and DDAH1 and DDAH2 expression in the liver. Loganic acid increased DDAH1 expression to a lesser extent but did not affect DDAH2 expression. Anthocyanins and loganic acid significantly increased mRNA expression of eNOS in the thoracic aorta; reversed blood glutathione levels consumed by dietary cholesterol. There was no remarkable difference in plasma MDA and superoxide dismutase (SOD) levels between the groups [91].

4.7. Aldose reductase inhibitory effect

Miláčková et al. evaluated the inhibitory activity of the aqueous extract of *C. mas* leaves on aldose reductase. The infusion of the leaves was lyophilized and used in the experiments. Aldose reductase enzyme was obtained from rat lenses. A low concentration of *C. mas* extract (50 μgmL^{-1}) showed aldose reductase inhibitor and antioxidant effect; higher concentrations (100 μgmL^{-1}) showed moderate pro-oxidant effect [92].

4.8. Cardioprotective effect

In an *in vivo* study, the cardioprotective activity of *C. mas* aqueous-alcoholic fruit extract against carbon tetrachloride-induced cardiotoxicity was investigated. For this purpose, albino rats were divided into 6 groups (n=6): i: sham (16 days normal diet and 16 days olive oil, 1 $mLkg^{-1}$, i.p.); ii: control (16 days normal diet and 16 days olive oil: carbon tetrachloride (1:1), 1 $mLkg^{-1}$, i.p.), iii and iv: pre-administration groups (300 and 700 $mgkg^{-1}$ extract respectively, for 16 days and day 16 olive oil: carbon tetrachloride (1:1), 1 $mLkg^{-1}$, i.p.); v and vi: post-administration groups (16 days normal diet and 16 days olive oil: carbon tetrachloride (1:1), 1 $mLkg^{-1}$, 300 and 700 $mgkg^{-1}$ extract after i.p. administration (2, 6, 12, 24, and 48 hours). Administration of carbon tetrachloride (1 $mgkg^{-1}$, i.p.) to mice resulted in a significant increase in both

plasma creatine kinase and lactate dehydrogenase enzymes. Myocardial lipid peroxidation products increased after carbon tetrachloride administration compared to the control group. There was a notable decrease in catalase, glutathione peroxidase (GPx) and SOD activities ($p<0.05$). The extract given prior to carbon tetrachloride administration had a significant decrease in myocardial lipid peroxidation products. The results showed that *C. mas* aqueous-alcoholic fruit extract displayed a cardioprotective effect by regulating the bioenergetic state of cardiac tissue [93].

4.9. Hepatoprotective effect

Potential activity of *C. mas* fruit extract on carbon tetrachloride-induced hepatotoxicity in male rats was evaluated by assessing parameters such as serum enzyme levels, albumin, total protein and liver lipid peroxidation. Carbon tetrachloride was injected to the rats (1:1, i.p.) to induce *in vivo* hepatotoxicity model. Methanol: water (7:3) extract was prepared from *C. mas* fruits. Male Wistar albino rats were divided into 5 groups (n=6); i: normal control group; ii: hepatotoxicity-induced control group (carbon tetrachloride-induced hepatotoxicity and water-only); iii: hepatotoxicity-induced and *C. mas* fruit extract treated (200 $mgkg^{-1}$); iv: hepatotoxicity-induced and *C. mas* fruit extract treated (500 $mgkg^{-1}$); v: positive control group (100 $mgkg^{-1}$ silymarin). *C. mas* fruit extract was applied to the animals for 14 days (p.o.). Blood enzyme samples (AST, ALT and ALP), total serum protein and liver lipid peroxidation remarkably decreased compared to the control group ($p<0.05$). This effect of *C. mas* was thought to be due to the membrane-stabilizing effects of antioxidant compounds in the extract. The results confirmed the use of *C. mas* in the treatment of liver problems among the general population [94].

Sangsefidi et al. examined the effect of *C. mas* fruit extract on liver function in nonalcoholic fatty liver disease in a double-blind randomized clinical trial. Fifty patients were assigned to groups to receive 20 ml of extract or placebo for 12 weeks. Aspartate aminotransferase, serum alanine aminotransferase, cytokeratin 18, aspartate aminotransferase levels and fibrosis, and steatosis scores were investigated. According to the results, although a remarkable decrease was observed in CK-18 levels among the *C. mas* extract group, there was no significant difference between the study groups. Fibrosis scores increased significantly in the placebo group. There was also a significant difference in fibrosis scores and changes between the *C. mas* extract and placebo groups [95].

4.10. Nephroprotective effect

In an *in vitro* study, it was aimed to assess the protective effect of the fruit extract of *C. mas* against cisplatin-induced nephrotoxicity. Renal epithelial cells (Vero) were incubated with *C. mas* fruit extract or with cisplatin or a mixture of cisplatin and *C. mas* fruit extract for 4 hours. Cell viability was determined by Methylthiazole Diphenyl Tetrazolium (MTT) method. Glutathione (GSH), SOD, MDA, and GPx levels were evaluated. Cell viability was found to be 42% in cells exposed to cisplatin and 59% in the case of *C. mas* fruit extract in combination with cisplatin. Cell damage and MDA concentration were significantly higher, GSH concentration, GPx and SOD enzyme effects were notably lower in cisplatin-treated cells ($p<0.05$). However, it was found that the harmful effects of cisplatin were remarkably reduced in the group treated with *C. mas* fruit extract [96].

The protective effect of aqueous methanol extract prepared from *C. mas* fruits on carbon tetrachloride-induced nephrotoxicity-induced rats was investigated. Male albino rats were divided into 7 groups consisting of 6 animals in each group, i: sham group; ii: normal control group; iii: carbon tetrachloride-induced nephrotoxicity group (1 $mLkg^{-1}$ in 80% olive oil), iv and v: test groups (prior to nephrotoxicity, *C. mas* fruit extract administered at doses of 300 $mgkg^{-1}$ and 700 $mgkg^{-1}$, respectively); vi and vii: test groups (after nephrotoxicity, *C. mas* fruit extract administered at doses of 300 $mgkg^{-1}$ and 700 $mgkg^{-1}$, respectively). Carbon tetrachloride administration to rats significantly increased creatinine level ($p<0.05$); urea, uric acid, protein and albumin levels. These parameters improved significantly in rats who received *C. mas* fruit extract ($p<0.05$). Antioxidant enzyme activity in the control group was lower than in the normal group. It was observed that the activities of these enzymes increased significantly in the treatment groups (before and after) ($p<0.05$). Glomerular and tubular damage by lipid peroxidation induced by carbon tetrachloride injection improved in the groups treated with fruit extract of *C. mas* [97].

4.11. Neuroprotective effect

Francik et al. investigated the neuroprotective effect of *C. mas* fruits in rat brain tissue. Freeze-dried *C. mas* fruits were given as dietary supplements to rats fed the control diet or fructose diet or high fat diet. The neuroprotective activity was investigated by determining antioxidant parameters (catalase, iron degradability, paraoxonase, protein carbonyl groups and free thiol groups) in rat plasma and brain tissue. The results showed that both fructose diet and high fat diet affect the antioxidant capacity. It was found that *C. mas* fruits increased catalase and paraoxonase activity in the brain tissue by reducing the number of free radicals in the brain tissue [98].

The effects of *Morus rubra* L. and *C. mas* extracts on penicillin-induced epileptiform were evaluated. Fruit juices were obtained by expression from fruits and expressed as dry weight (g), gallic acid (mg) equivalent. Rats were randomly divided into 10 groups, each containing 6 animals: control, sham, penicillin, penicillin + *M. rubra* (2.5; 5; 10; 20 $mgkg^{-1}$) and penicillin + *C. mas* (2, 5; 5; 10 $mgkg^{-1}$). Penicillin (500 IU, intracortical) was used for the induction of epileptiform activity, and electrocorticogram recordings (150 min) were obtained. Biochemical analyzes were also performed on blood samples. According to the electrocorticogram analysis, the effective dose was 10 $mgkg^{-1}$ for both *C. mas* and *M. rubra*. In erythrocyte studies, significant differences were found in terms of nitric oxide in sham, control and penicillin groups ($p=0.001$). No statistically significant difference was found between penicillin + *M. rubra* and penicillin + *C. mas* groups ($p>0.05$). In all groups, significant differences were found when MDA levels in erythrocytes and plasma were evaluated ($p<0.001$). MDA value was the highest in the penicillin group (37.193 $\mu molg^{-1}$ Hgb) and the lowest in the *C. mas* group (24.488 $\mu molg^{-1}$ Hgb). Significant differences were detected in plasma between the penicillin + *C. mas* and penicillin + *M. rubra* groups in terms of xanthine oxidase ($p=0.008$). It was determined that both extracts decreased the frequency of epileptiform effect [99].

4.12. Radioprotective effect

Leskovac et al. investigated the radioprotective effects of phytochemically characterized *C. mas* aqueous methanol leaf extract on human lymphocytes. Blood samples were collected from three non-smoking male donors for *in vitro* study. To determine the optimum dose, the effect of plant extract was examined using doses of 100-400 µg in non-irradiated samples. Amifostine was used as positive control and no significant change was observed. Heparinized blood samples were taken into test tubes and exposed to 0.45 $Gymin^{-1}$ gamma irradiation at 2 Gy dose. Micronucleus, thiobarbiturate and apoptosis tests were performed to examine the radioprotective effect. The extracts (0.1 to 0.4 $mgmL^{-1}$) were applied to the cell cultures. It was determined that the lowest dose had the best protective effect. *C. mas* extract showed a decrease in radiation-induced micro-nucleus incidence (19.23%) and lipid peroxidation products (50.04%) and a two-fold increase in apoptosis without causing any irregularity in the cell cycle as well as a gradual decrease in cell proliferation [100].

4.13. Protective effect on reproductive system

Protective activity of *C. mas* methanol extract and vitamin E on the sperm quality of methotrexate-treated mice was investigated. 48 mice in the experiment were divided into the groups as follows: i: control group (saline only); ii: methotrexate group (weekly methotrexate, 20 $mgkg^{-1}$, 5 weeks); iii, iv and v: experimental groups (methotrexate once weekly (20 $mgkg^{-1}$) and *C. mas* fruit extract at doses of 1000, 500 and 250 $mgkg^{-1}$ per day, respectively); vi: the reference group (methotrexate once weekly (20 $mgkg^{-1}$) and vitamin E (100 IU per day). Total antioxidant capacity, sperm count, motility, viability and morphology, and DNA damage were evaluated. It was determined that *C. mas* fruit extract prevents negative changes in methotrexate-induced sperm quality and has a protective effect against DNA damage [101].

4.14. Cytotoxic effect

The selective anticancer effects of aqueous-alcoholic extract *of C. mas* fruits on different human cancer cells were investigated. Cytotoxic activity of *C. mas* fruit extract (0, 5, 20, 100, 250, 500, 1000 μgmL^{-1}) on A549 (non-small cell lung cancer), MCF-7 (breast adenocarcinoma), SKOV-3 (ovarian cancer) and PC-3 (prostate adenocarcinoma) cell lines was investigated by using MTT method. Remarkable differences ($p<0.05$ and $p<0.001$) were found in all tested doses (5-1000 μgmL^{-1}) compared to the negative control group. *C. mas* fruit extract decreased cell viability to less than 26% in cancer cell lines, even at the lowest dose. The IC_{50}

value was found to be less than 5 µgmL^{-1}. *C. mas* showed inhibitory effect in SKOV-3, MCF-7, PC-3 and A549 cell lines, with the inhibition rates of 81.8%, 81.9%; 81.6% and 79.3%, respectively [102].

In another study, the antiproliferative effect of infusion prepared from the leaves of *Cornus* species was investigated. The antiproliferative effects of the extracts (at doses of 50-750 µgmL^{-1} and at the 24th, 48th, 72nd hour) on MCF-7 were evaluated, and the *C. mas* aqueous extract showed significant antiproliferative effect on MCF-7 cells (11.1% after 72 hours). It was suggested that this effect may be due to the tannins and polyphenolic compounds [103].

Šavikin et al. investigated the cytotoxicity of methanol extracts of *C. mas* against cervix adenocarcinoma (HeLa) and human colon carcinoma (LS174) cell lines. At the dose of 200 µg/mL, the flower and leaf extracts exhibited good activity in both cell lines [104].

4.15. Anti-colitis activity

Süntar et al. investigated the activity of the extracts and sub-extracts prepared from *C. mas* fruits on trinitrobenzenesulfonic acid (TNBS)-induced ulcerative colitis model in rats. Sulfasalazine was used as a standard. According to the results, the increase in daily feed consumption and body weight were determined to be the highest in 80% methanol extract at a dose of 400 mg/kg, *n*-butanol sub-extract and the reference. It was observed that the fecal form was yellow-slippery in all groups and returned to normal after treatment with *C. mas* extracts. The rectal prolapse score was determined less in the groups treated with the extract (400 mgkg^{-1} bw and *n*-butanol sub-extract). The 80% methanol extract (400 mgkg^{-1}) and *n*-butanol sub-extract provided the best recovery based on wet weight measurements and column damage scoring on the removed colon tissues. The best healing was achieved with 80% methanol extract of 400 mgkg^{-1} and *n*-butanol sub-extract based on wet weight measurements and colon damage scoring [105].

5. TOXICITY STUDIES ON *CORNUS MAS* L.

West et al. investigated the potential toxicity of *C. mas* fruits. Three female rats were used to determine the possible toxicity. The animals fasted before the experiment and 5 mLkg^{-1} of extract was given daily by the intragastric route on the day of the experiment. Immediately after administration on day 0, animals were observed for 4 hours for symptoms of toxicity and death. Observations were made only once daily for the following two weeks (1-14 days). During the experiment, possible skin, eye, and mucosal abnormalities, secretions, diarrhea, and behavioral changes in animals were observed. Animals were weighed on day 0 before dosing and on days 7 and 14. For *C. mas*, the acute oral toxicity test indicated no signs of death or side effects, nor tissue or organ abnormalities. *C. mas* was reported to have LD_{50} greater than 5200 mgkg^{-1} and no toxic effect. In reverse mutation testing, it was determined that *C. mas* fruits do not have a genotoxic effect [106]. Es Haghi et al. stated that water extract of *C. mas* fruits supplementation at the doses of 100-1650 mg/kg for 2 weeks showed no toxicity in mice and LD_{50} value was found 1270 mg/kg [97]. In another study on dyslipidemic children and adolescents to investigate amelioration of lipid profile and vascular inflammation of *C. mas* supplementation, patients were given 50 g of *C. mas* twice a day. According to the results, no toxic effect of fresh *C. mas* fruit consumption was observed at a dose of 100 g/day for 6 weeks [107]. Soltani et al. evaluated the administration of fruit extract of *C. mas* in adult diabetic patients for 6 weeks. The extracts equivalent to 600 mg of anthocyanins daily did not show any adverse effects [84]

6. CONCLUSION

C. mas is a very promising plant due to its rich phytoconstituents. There are numerous studies on *C. mas* in the literature. Its secondary metabolites, including flavonoids, phenolic acids, organic acids, anthocyanins, tannins, fatty acids, iridoids and carotenoids, are responsible for various biological activities. *C. mas* is also used as a safe medicinal plant in folk medicine. This plant has been found to be a good source of antioxidants, which supports its traditional uses. In addition, antimicrobial, anti-inflammatory, antioxidant, antidiabetic, antiatherosclerotic, antihyperlipidemic, neuroprotective, hepatoprotective, cardioprotective, nephroprotective, and cytotoxic activities have been demonstrated. The antimicrobial and antioxidant activities of *C. mas* have been particularly emphasized in the literature, and these studies have generally focused on the fruit parts. The most commonly detected secondary metabolites in the plant are flavonoids and anthocyanins.

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