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Determination of in Vitro Antioxidant, Antimicrobial Properties and COX-1/COX-2 Enzyme Inhibition Activity of *Capparis Sicula*

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ABSTRACT

Since synthetic drugs cause many side effects and have a high cost, there has been increasing interest in the development of herbal-based drugs that have fewer side effects and are relatively inexpensive. *Capparis sicula* is traditionally used in the treatment of some diseases among people. For this purpose, the antioxidant and antimicrobial properties of the methanol extract of the *Capparis sicula* plant and its inhibitory effects on COX-1 and COX-2 enzymes were investigated. In the study, the antioxidant properties of the *Capparis sicula* plant were determined by DPPH and CUPRAC methods, while its antimicrobial properties were determined by the disk diffusion method. The effect of *Capparis sicula* on COX-1 and COX-2 enzymes was determined colorimetrically using commercial kits. The results showed that *Capparis sicula* had a significant antioxidant effect, but did not have any antimicrobial effect on standard strains of *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* and *Candida albicans*. In addition, the inhibitory effect on the COX-1 enzyme was 4.23% for the first time, and the inhibition effect on the COX-2 enzyme was determined as 23.21%. As a result, the pharmaceutical, food and cosmetic industries can use *Capparis sicula* as an important source of natural raw materials.

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Capparis sicula'nın in vitro Antioksidan, Antimikrobiyal Özellikleri ve COX-1/COX-2 Enzim Inhibisyon Aktivitesinin Belirlenmesi

ÖZET

Sentetik ilaçlar birçok yan etkiye ve yüksek maliyete neden olduğundan daha az yan etkisi olan ve nispeten daha ucuz olan bitkisel bazlı ilaçların geliştirilmesi artan bir ilgi görmüştür. *Capparis sicula* halk arasında bazı hastalıkların tedavisinde geleneksel olarak kullanılmaktadır. Bu amaçla sunulan çalışmada *Capparis sicula* bitkisinin metanol ekstraktının antioksidan ve antimikrobiyal özellikleri ile COX-1 ve COX-2 enzimleri üzerindeki inhibisyon etkileri araştırılmıştır. Çalışmada *Capparis sicula* bitkisinin antioksidan özellikleri DPPH ve CUPRAC yöntemleri ile belirlenirken, antimikrobiyal özellikleri disk difüzyon yöntemi ile belirlenmiştir. *Capparis sicula*'nın COX-1 ve COX-2 enzimleri üzerindeki etkisi ise, ticari kitler kullanılarak kolorimetrik olarak belirlendi. Sonuçlar, *Capparis sicula*'nın önemli bir antioksidan etkiye sahip olduğunu, ancak standart *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* ve *Candida albicans* suşları üzerinde herhangi bir antimikrobiyal etkiye sahip olmadığını gösterdi. Ayrıca COX-1 enzimi üzerindeki inhibisyon etkisi ilk kez

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%4.23, COX-2 enzimi üzerindeki inhibisyon etkisi ise %23.21 olarak tespit edilmiştir. Sonuç olarak, ilaç, gıda ve kozmetik endüstrileri, *Capparis sicula*'yı önemli bir doğal hammadde kaynağı olarak kullanabilir.

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INTRODUCTION

Capparis is a plant belonging to the Capparidaceae family, that can survive for many years and has been used by people for centuries to heal disease and its symptoms. The *Capparis* plant is also known as bubu, gebre, kapari, kebere, and pickle herb in different parts of Turkey (Duman & Özcan 2014). Numerous studies have reported that *Capparis* is effective in pain relief, anti-diarrhoea, treatments for allergies, infections, diuretic and diabetes-related symptoms (Singh et al. 2011; Tlili et al. 2010; Tlili et al. 2011; Argentieri et al. 2012; Arslan & Bektaş 2010; Bektaş et al. 2012a; Boga et al. 2011; Husseini et al. 2013).

Capparis sicula (C. sicula) is a shrub that is widely distributed in Mediterranean countries. Since antiquity, people in Greece have been using the tips of the *C. sicula* to make a sauce. People living in Mediterranean countries have used it as a condiment for many years (Inocencio et al. 2000). *C. sicula* is widely used in Turkey. People in and around Adana, a large city in southern Turkey, use its buds in particular as an analgesic. In this region, people crush its flower and bud parts and wrap them around their kneecaps to alleviate joint pain. In addition, it is used to treat rheumatic diseases and inflammation of the lung, and *C. sicula* has a significant enzyme inhibitory property (Dafni et al. 1984; Mahasneh et al. 1996; Abbas et al. 1992; Marrelli et al. 2014). For this reason, it is important to determine the inhibitory effect of *C. sicula* on COX-1 and COX-2 enzymes.

Cyclooxygenase enzymes (COXs) catalyze two reactions. One combines arachidonic acid (AA) with the oxygen molecule to form prostaglandin G_2 (PGG_2), and the other is the conversion of PGG_2 to prostaglandin H_2 (PGH_2). COXs perform an important initial reaction in the AA metabolic pathway, resulting in the generation of proinflammatory prostaglandins, thromboxanes, and prostacyclins. Prostaglandins regulate the contraction of smooth muscles in metabolism, blood pressure, and platelet aggregation. In addition, their overexpression causes pain and fever (Lee et al. 2003). Three isoforms of the COX enzyme are known, namely COX-1, COX-2, and COX-3. Of these, COX-1, as a constitutive enzyme, is responsible for protecting the gastric mucosa, regulating platelet aggregation, and synthesizing prostaglandins responsible for renal blood flow, while COX-2 has been reported to be prominent in oncogenesis, pain, and inflammation. Since NSAIDs used in the treatment of inflammation inhibit COX-1, and COX-2, they have been reported to cause gastrointestinal ulceration, kidney damage, and hepatic side effects in long-term use (Abdu-Allah et al.2020; Khoshneviszadeh et al. 2016)

Inflammation is part of the body's defense mechanisms, where metabolism is initiated as a protective response against pathogens, foreign bodies, or injury (Raikar & Shingade, 2018). It can also be a symptom of infections that can be detected after their symptoms have been observed (Panda et al. 2020). NSAIDs are known to reduce inflammation. They are used to heal some diseases caused by inflammation, such as rheumatoid arthritis, and fever, and to relieve daily pain (Bindu et al. 2020). There are many drugs on the market to treat inflammatory diseases. But very few of them are non-toxic. Gastrointestinal problems that develop upon the use of anti-inflammatory drugs are a dilemma for the medical world, today. In this context, comprehensive studies conducted using ethnobotanical plants with anti-inflammatory and analgesic properties are critical for opening new horizons in the treatment of inflammatory diseases (Igbe et al. 2010).

Therefore, investigating plant extracts' ability to inhibit enzymes can help us discover compounds that could effectively treat various diseases (Liu et al. 2018; Orhan et al. 2017). It is a very old practice to use herbs and plant extracts to prevent infections; however, the effects of most of them have not been scientifically proven (Ellof 1998). In addition, currently, there is little information available [to us] on how and which parts of these plants are good for treating various diseases. For this reason, it is recommended to conduct further scientific studies to support traditionally used plants and develop new natural products against the harms of synthetic products (Özcan 2020). From the literature review, it has been seen that the number of studies on the biological properties and traditional use of *C. sicula* is limited.

The present study was conducted to investigate the antioxidant and antimicrobial properties of *C. sicula* and its effect on COX-1 and COX-2 enzymes.

MATERIALS and METHODS

Plant Samples and Preparation of Plant Extracts

The plant samples were collected from the pine groves of the region known as Kemal Hill, between Karaömerli and Kılbaş Villages in Adana Province, between May and July 2020. The scientific diagnosis of *C. sicula* was made by Mehmet FIRAT, a lecturer at Yüzüncü Yil University, Faculty of Education, Department of Biology. Flora of Turkey and the East Aegean Islands was the primary source for scientific plant identification (Güner et al. 2000).

Preparation of Plant Extracts

After the plants were dried without exposure to sunlight, they were broken into small particles with the help of a hand blender. Then, a methanol extract was prepared from its flower buds (10 g 100 mL^{-1}). The solvent was removed from the medium with the help of an evaporator. The ready-to-use extracts were used fresh.

Antioxidant Assays

Free Radical Scavenging Activity (DPPH)

The free radical scavenging activity of DPPH (2,2-diphenyl-1-picrylhydrazyl, free radical) was performed with minor modification according to the method specified by Brand-Williams et al. (1995). As a free radical, 10^{-4} M DPPH was prepared in methanol. 0.02, 0.04, 0.06, 0.08, 0.10 g mL^{-1} and 3.9 ml of DPPH solution were added into the test tubes, respectively, and the mixtures were incubated for 30 minutes in a dark environment at room temperature. At the end of the incubation, their absorbance at 517 nm against the blank (methanol) was read using the spectrophotometer. The amount of DPPH removed from the reaction medium was calculated with the following formula. Experiments were carried out three times.

% Inhibition = $[(A_0 - A_1)/A_0] \times 100$.

A_0 refers to control absorbance, A_1 refers to the absorbance of the sample.

Determination of Total Antioxidant Capacity (TAC) by CUPRAC Method

In a glass tube, 1 mL of copper (II) solution, neocuproine solution and ammonium acetate buffer were added sequentially. 10 µL of solutions prepared at different concentrations of *C. sicula* extract (0.02-0.10 g mL^{-1}) as well as distilled water were added to the same tube. The total volume was made up of 4 mL. The resulting solution was kept closed for 30 minutes at room temperature. The absorbance value was measured at 450 nm (Apak et al. 2004). Ascorbic acid (AsA) was used as a standard and was prepared as 4.4 $x10^{-4}$ M. Total antioxidant capacity was calculated based on AsA. The experiments were carried out three times.

Determination of Antimicrobial Properties

Antimicrobial activity was investigated according to the disk diffusion method (NCCLS 1997). *Staphylococcus aureus* (ATCC 33862), *Pseudomonas aeruginosa* (ATCC 27853), *Escherichia coli* (ATCC 35218), *Candida albicans* (ATCC 90028) standard strains were activated by inoculating Mueller Hinton Broth (OXOID) and fungal strains in Sabouraud Dextrose (SD) Broth (DIFCO) and incubated for 24 hours at 35±2°C. Their concentrations were adjusted according to MCFarland 0.5 (108 CFU mL^{-1}) (Barry & Thornsberry 1985). Bacteria Mueller Hinton Agar (OXOID) and yeast fungus Sabouraud Dextrose (SD) Agar (OXOID) were left on the media for 15 minutes before being applied with a glass baguette. 25 µl of plant extracts were absorbed into 6 mm diameter sterile standard discs and left in the culture medium (Barry & Thornsberry 1985). Afterwards, the samples were incubated for 24 hours at 37 ºC and their inhibition diameters were determined. The extract with the highest concentration was used to determine the antimicrobial effect. The standard strains used in the study were obtained from the Public Health Institution of Turkey.

Detection of COX-1 and COX-2 Enzyme Inhibition

The inhibition capacity of COX enzymes was determined by using commercial kits (COX ovine/human, Inhibitor Screening Assay Kit item No. 560131). Results were read at 415 nm on a Micro Elisa plate reader (Bio-Tek). Calculations were made according to the Kit procedure. In the COX enzyme inhibition experiments, the extract prepared at a concentration of 0.10 g mL^{-1} was used by diluting 10 times.

RESULTS and DISCUSSION

The World Health Organization (WHO) reports that 80% of the world's population benefits from medicinal plants for their health needs. In addition, the active substance in 20% of commercial drugs is of plant origin (Gurib-Fakim 2006). Extraction and analysis of plants are vital for discovering new drugs and modernising existing formulations (Arulmozhi et al. 2019a). Alternatively, there is an increasing interest in research on natural antioxidants because of the toxic effects of existing synthetic antioxidants on the liver and their carcinogenicity (Grice 1986; Wichi 1988).

For this purpose, in the presented study, the antioxidant properties of methanol extracts (0.02-0.10 mg mL^{-1}) of the *C. sicula* plant prepared at different concentrations were determined by DPPH and CUPRAC tests. In the DPPH test, it was determined that the antioxidant property increased due to the increase in concentration compared to the control group (Figure 1).

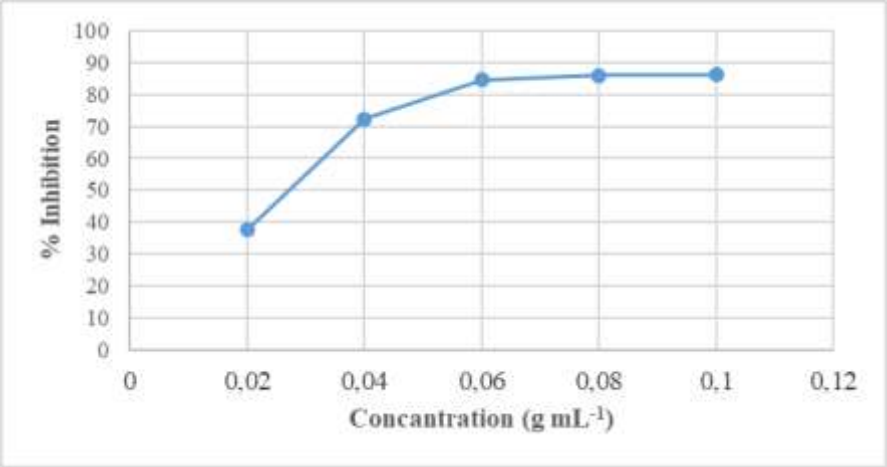

Figure 1 DPPH scavenging activity of *C. sicula* plant extract at different concentrations. The average of three measurements for each concentration was taken

Şekil 1. Farklı konsantrasyonlarda C. situla akstraktlarının DPPH temizleme aktivitesi. Her konsantrasyon için üç ölçümün ortalaması alındı.

AsA was used as a standard in the analyses performed by the CUPRAC method. A single concentration of AsA was used, and the TAC value was found to be 0.206 ± 0.062 (mmol AsA g^{-1}). It was determined that the *C. sicula* plant reached higher values than AsA at the concentrations of 0.02 and 0.04 g mL^{-1}. These results show that *C. sicula* has an important antioxidant capacity (Table 1).

Table 1 CUPRAC test antioxidant activity results of *C. sicula* extract and AsA. Each value is shown as X±SD (n=3).

Çizelge 1. C. sicula ve AsA CUPRAC test antioksidan aktivite sonuçları. Her değer X±SD olarak gösterilmiştir (n=3).

C. sicula (g mL^{-1})	**PLUG (mmol AsA /g- *C. sicula*)**	**A(M)**	**PLUG (mmol AsA /g-AsA)**
0.02	0.216 ± 0.107		
0.04	0.210 ± 0.096		
0.06	0.142 ± 0.107	$4.44x10^{-4}$	0.206 ± 0.062
0.08	0.175 ± 0.154		
0.10	0.185 ± 0.181		

In parallel with the results obtained from the present study, Subramanian & Ramani (2020) examined the antioxidant activities of 4 different extractions of the *Capparis brevispina* DC plant, and they determined that the IC_{50} value of the ethanol extract was 37.23 µg mL^{-1}, the IC_{50} value of the water extract was 41.78 µg mL^{-1}, the IC_{50} level of the chloroform extract was 42.44 µg mL^{-1}, and hexane extract was 56.34 µg mL^{-1}. Preetha et al. (2020) investigated the antioxidant effect of ethanolic and hydroethanolic extracts of *Capparis decidua* fruits in their study and showed that plant fruits exhibited a very good antioxidant activity compared to the control group (Preetha et al., 2020).

In a study examining the antioxidant activities of ethanol and water extracts of *C. spinosa* subsp. *spinosa* var. *spinosa*, *C. aegyptia*, *C. zoharyi*, *C. ovata* subsp. *ovata*, *C. sicula* subsp. *sicula* and *C. orientalis* plants by DPPH and ABTS tests, it was reported that the plants showed an antioxidant activity at varying rates. In the same study, the IC_{50} value of the leaves of the *C. sicula* subsp *sicula* grown in Tunisia was found to be 74.78 g mL^{-1} by the DPPH test. After the *C. sicula* subsp *sicula* plant was examined with the ABTS method, the IC_{50} value of its ethanolic extract was found to be 62.63 g mL^{-1} (Aichi-Yousfi et al. 2016). In addition, lyophilized and methanolic extracts of *C. spinosa* have been reported to have significant antioxidant effects (Bonina et al. 2002).

Assadi et al. (2021) reported that *C. spinosa* fruit

extracts showed antioxidative and antidiabetic effects in experimentally induced type 2 diabetes in rats administered with high fat and low dose streptozotocin. In the study conducted by Tlili et al. (2017) on rats treated with CCl_4, they noted that methanol extracts of *C. spinosa* leaves decreased the level of malondialdehyde (MDA), and their results supported the use of this herb, which is traditionally used in the prevention of kidney and liver diseases.

Plant-based medicines have been used by humans in the treatment of diseases for a long time. Plants have always been the source of new medicines (Ganapathy 2017). In the last twenty years, many scientists have discovered new antimicrobial agents from different natural sources (Vidya et al. 2012). In recent years, pathogenic microorganisms have become more resistant to current antibiotics due to their overuse. Therefore, further studies are needed to discover more economical antimicrobial agents with less toxicity (Arulmozhi et al. 2018).

In the presented study, methanol extracts of *C. sicula* flower buds did not show any antibiotic effect on microorganisms at the studied concentrations (Table 2.).

Table 2. Results of antimicrobial effect of *C. sicula*
Çizelge 2. C. situla'nın antimikrobiyal sonuçları

C. sicula (g mL^{-1})	**Microorganism**	**Antimicrobial Effect**
0.10 g mL^{-1}	*Staphylococcus aureus* (ATCC 33862)	-
	Pseudomonas aeruginosa (ATCC 27853)	-
	Escherichia coli (ATCC 35218)	-
	Candida albicans (ATCC 90028)	-

Unlike the obtained data, Arulmozhi et al. (2019) showed the antimicrobial effect of leaf extracts of the *C. zeylanica* plant on six pathogenic organisms, including *Staphylococcus epidermidis, Enterococcus faecalis, Salmonella paratyphi, Shigella dysen-teriae, Mycobacterium tuberculosis,* and *Candida albicans*. They reported that the plant had an antimicrobial effect on all strains in the study.

Preetha et al, (2020) reported in their study investigating the antimicrobial effect of ethanolic and hydroethanolic extracts of *Capparis decidua* fruits that plant fruits showed very good antimicrobial effects on strains of *Enterococcus faecalis, Klebsiella pneumonia, Pseudomonas aeruginosa, Streptococcus mutans* and *Escherichia coli.* Mazarei et al. (2017) reported that *Capparis spinosa* L. leaf polysaccharides showed antioxidant activity in the DPPH test. In addition, they showed that the antimicrobial effect of the polysaccharides on gram-negative bacteria consisting of *Escherichia coli*, *Shigella dysenteriae* and *Salmonella typhi* was higher than the effect on gram-positive bacteria of *Bacillus panis* and *Staphylococcus aureus*. In their antimicrobial study, Subramanian & Ramani (2020) showed that different *C. brevispina* extracts had minimal inhibition against gram-negative bacteria (*Escherichia coli* MTCC 739 and *Pseudomonas aeruginosa* MTCC 2453) and selected fungi (*Aspergillus niger* MTCC 5889 and *Aspergillus flavus* MTCC 9390). But in the same study, they reported the presence of resistance to gram-positive bacteria (*Bacillus subtilis* MTCC 2423; *Staphylococcus aureus* MTCC 2940). In their study, Anjuma et al. (2020) investigated the antibacterial effect of the methanolic extract of *Capparis decidua* and found that the floral particles of the plant had an antimicrobial effect on *E. cloacae* (MIC 250 lg mL^{-1}), *K. pneumonia* (MIC 250 lg mL^{-1}), *S. paratyphi* (MIC 1000 lg mL^{-1}), *S. typhi* (MIC 500 lg mL^{-1}) and *S. marcescens* (MIC 250 lg mL^{-1}). Moreover, in the same study, it was determined that the aerial parts of plant had an antimicrobial effect on pathogenic microorganisms including *A. junii* (MIC 250 lg mL^{-1}), *E. cloacae* (MIC 250 lg mL^{-1}), *E. coli* (MIC 250 lg mL^{-1}), *M. luteus* ATCC-4617 (MIC 250 lg mL^{-1}), *P. vulgaris* (MIC 250 lg mL^{-1}), *P. aeruginosa* (MIC 250 lg mL^{-1}), *S. paratyphi* (MIC 500 l g mL^{-1}), *S. typhimurium* (MIC 250 lg/mL), *S. dysenteriae* (MIC 250 lg mL^{-1}), and *S. aureus* (MIC 500 lg mL^{-1}). The difference in the results of the present study may be due to the concentration used, as well as the soil and climatic conditions in the region where the plant grows.

NSAIDs are drugs that are frequently used in the treatment of pain, inflammation, and fever, and they show an important therapeutic effect in curing inflammatory diseases (Vonkeman et al. 2010). It is thought that the action mechanism of these drugs depends on the inhibition of COX enzymes (Ulbrich et al. 2002). There are two main isoforms of the COX enzyme. COX-1 is a structural enzyme found in normal tissues. COX-2, on the other hand, is an inducible enzyme that is rarely expressed under physiological conditions and is increasingly expressed in inflammation and tumorigenesis. Arachidonic acid is synthesised by COX-2 to prostaglandin E_2 and a number of inflammatory mediators are

synthesised. Therefore, COX-2 is an important enzyme in inflammatory events (Zhang et al. 2013). In addition, it has been reported that expensive and selective COX-2 inhibitors have side effects (Emery et al. 1999). Alternatively, safer and cheaper drugs can be developed from medicinal plants (Gautam & Jachak, 2009).

In the present study, the inhibitory effect of methanol extracts of *C. sicula* flower buds on COX-1 and COX-2 enzymes was determined for the first time. While the *C. sicula* methanol extract inhibited the COX-1 enzyme by 4.23%, it inhibited COX-2 by 23.21% (Table 3). The inhibitory effect of methanol extract on COX-2 was 5.48 times greater than its effect on COX-1.

Table 3. COX-1 and COX-2 % inhibition values of methanol extract of *C. sicula* plant
Çizelge 3. C. sicula bitkisinin metanol ekstraktının COX-1 ve COX-2 % inhibisyon değerleri.

Enzyme	inhibitor	% Inhibition Value
COX-1	*C. sicula*	4.23%
COX-2	*C. sicula*	23.21%

Likewise, a study conducted on mice reported that ethanol, and the water extracts of the leaves of *Capparis zeylanica* showed dose-dependent analgesic effects and water extract was more effective than the ethanol extract (Ghule et al. 2007). Tekulu et al. (2020) reported that the extracts obtained from the roots of the plant *Capparis tomentosa* Lam showed anti-inflammatory effects. Bektaş et al. (2012a) investigated the anti-inflammatory effect of the *Capparis ovata* plant and found that the fruits of the plant and methanol extracts of its flower buds showed a significant anti-inflammatory effect. In their study, they found that both extracts showed a significant inhibitory effect in the prostaglandin E_2 inflammation model (Bektaş et al. 2012b). In a study on mice, it was reported that natural products obtained from *Capparis ecuadorica* HH (Capparaceae) had great anti-inflammatory potential as they blocked the inflammatory response in (LPS)-indued RAW 264.7 cells (Song et al. 2020). In their study, Rahimi et al. (2020) reported that *C. spinosa* reduced brain inflammation. In another study, it was reported that alcoholic extracts of *Capparis spinosa* exhibited a strong anti-inflammatory effect in rats. In the study, it was stated that this anti-inflammatory activity of alcoholic extracts was associated with the presence of polyprenols such as cappaprenol-12, cappaprenol-13, and cappaprenol-14 containing 12, 13, and 14 isoprenoid units, respectively (Al-Said et al. 1988). Various studies have stated that aqueous and chloroform extracts of *C. spinosa* indicated an anti-inflammatory effect on rats (Zhou et al. 2010; Ageel et al. 1986). In addition, it has been reported that the leaves, stems and roots of *Capparis erythrocarpos* plant have analgesic effects (Twumasia et al. 2019).

CONCLUSION

Consequently, it was determined that the methanol extract obtained from the flower buds of the *C. sicula* plant showed a high antioxidant effect but did not show any antimicrobial effect on the bacterial and fungal strains used in the present study. In addition, the inhibitory effect on COX-1 and COX-2 enzymes was detected *in vitro* for the first time. With this study, the high antioxidant capacity of *C. sicula* and its inhibitory effect on COX enzymes were clearly demonstrated. *C. sicula* may be a good alternative for use in the pharmaceutical, cosmetic, and food industries. However, further studies are needed for the safe and effective use of *C. sicula*.

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Contribution Rate Statement Summary of Researchers

The authors declare that they have contributed equally to the article.

Conflict of Interest Statement

The authors of the article declare that there is no conflict of interest between them.

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