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ORIGINAL ARTICLE / ORIGINALBEITRAG

The Effect of Total Anthocyanins Extracted From Sweet Cherry Cultivars on Carbonic Anhydrases and Antioxidant Activity

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Abstract
Total anthocyanins were extracted from eleven sweet cherry cultivars grown in Sakarya, Turkey. In vitro inhibition effects of extracted total anthocyanins on purified carbonic anhydrase I and II were investigated by using CO_2 as a substrate. The results showed that all extracted total anthocyanins inhibited the hCA I and hCA II enzyme activities. Among all cultivars, 'Merton Premier' was found to be the most active one against both hCA I (IC_{50} = 0.83 µg/mL) and hCA II (IC_{50} = 1.16 µg/mL). Additionally, the DPPH activities of the extracts were investigated as antioxidant properties. The results exhibited that 'Churchill' and 'Merton Premier' have high antioxidant activity with 74.102% and 73.503% DPPH activity, respectively.

Keywords Carbonic anhydrase · DPPH activity · Extraction · Sweet cherry cultivars · Total anthocyanins · Prunus avium

Einfluss von Anthocyanen aus Früchten verschiedener Süßkirschensorten auf die Carboanhydrase und die antioxidative Aktivität

Schlüsselwörter Carboanhydrase · DPPH Aktivität · Extraktion · Süßkirschensorten · Anthocyane · Prunus avium

Introduction

Fruits and vegetables are important in terms of nutrition and human health due to their low energy content, high content of minerals and vitamins (Sezgin 2014). The regular consumption of fruits and vegetables is widely recommended in dietary guidelines worldwide because of their richness in nutrients (Seraglio et al. 2018). The consumption of a sufficient amount of vegetables and fruits decreases the risk of many chronic diseases, such as cancer, cardiovascular diseases, hypertension, and digestive system diseases. It also provides strengthening of the immune system and delays ageing. Vegetables and fruits are the best sources of vitamin A, vitamin C and beta-carotene, especially for antioxidants.

Sweet cherry (*Prunus avium* L.) is one of the most popular table fruits (Correia et al. 2017) and a member of the Rosaceae family (Hewitt et al. 2017). Sweet cherry cultivars contain polyphenols consisting of flavonoids, flavan-3-ols, and flavonols and non-flavonoid compounds, such as hydroxycinnamic and hydroxybenzoic acids (Shirasawa et al. 2017). Additionally, cherries are rich in vitamin C, A, E, and K, carotenoids, especially β-carotene, lutein, and zeaxanthin. It has been reported that carotenoids (β-carotene, β-cryptoxanthin, and α-carotene) are found in sweet cherry fruit (Sezgin 2014). Important quality characteristics of cherry cultivars are weight, colour, firmness, sweetness, sourness, flavour, and aroma. Fruit maturity is one of the key factors determining overall fruit quality. Cherries should be harvested at the end of the maturation stage when they are fully ripe to ensure good eating quality. Aroma, flavour, sourness, sweetness, and texture are also

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essential attributes (Correia et al. 2017). Sweet cherry is an important crop, especially in Asia, Europe, and North America, which produced 910,928, 721,356 and 399,832 t of fruit each year, respectively. The five largest producers in the same year were Turkey (480,748 t), the United States (384,647 t), Iran (~150,000 t), Italy (104,766 t) and Spain (96,946 t) (Blando and Oomah 2019). Therefore, sweet cherry consumption could help to reduce the risk of arthritis (indicated by CRP, TNFα, IL-18 and IL-1Ra), cardiovascular disease (CRP, ferritin, ET-1, EN-RAGE, PAI-1 and IL-18), cancer (ET-1), and hypertension (ET-1) (Kelley et al. 2018). Finally, a single 280-g dose of fresh cherries administrated to healthy women was shown to reduce the levels of serum urate, which can cause gout when deposited in joint tissues (Commisso et al. 2017).

The carbonic anhydrases (CAs, EC 4.2.1.1) belong to a superfamily of metalloenzymes present in all life kingdoms and encoded by seven evolutionarily unrelated gene families: the α-, β-, γ-, δ-, ζ- η- and the last recently discovered θ-CAs (Angeli et al. 2018). CA is a very important enzyme, which regulates CO_2 levels in living organisms (Göcer et al. 2017). Carbonic anhydrases (CAs) are zinc metalloenzymes that catalyze the reversible hydration of carbon dioxide (CO_2) to produce bicarbonate (HCO_3^-) and a proton (H^+) ($CO_2 + H_2O \rightarrow HCO_3^- + H^+$) (Koutnik et al. 2017). CAs are expressed in numerous plant tissues and in different cellular locations (DiMario et al. 2017). Humans encode 15 α-class CA isoforms (Koruza et al. 2019). Among these, only 12 coordinate a zinc in the active site making them catalytically active (CAs I–IV, CAs VA–VB, CAs VI–VII, CA IX, and CAs XII–XIV). Isoforms CA VIII, X, and XI are termed CA-related proteins (CA-RPs) as they lack the required metal ion within the active site (Mboge et al. 2018). CA has active properties in the kidney, gastric mucosa, eye lens, salivary glands, brain, nerve myelin sheath, pancreas, prostate and uterus (Göcer et al. 2017). Inhibition of CA isoenzyme is important in the treatment of many diseases due to its role in diseases such as oedema, glaucoma, obesity, cancer, epilepsy, and osteoporosis (Zengin Kurt et al. 2019). Carbonic anhydrase inhibitors (CAIs) are in clinical use for the treatment of various diseases such as diuretics, glaucoma, epilepsy and more recently as antitumor and antimetastatic agents (Angeli et al. 2018).

Therefore, the designs of effective synthetic agents and extractions of natural bioactive compounds from various plants continues to be the focus of interest for scientists. Additionally, our groups have been evaluated the effects of synthetic or natural compounds on various enzymes and antioxidant activities (Kuday et al. 2014; Sonmez et al. 2014, 2019; Kurt et al. 2016, 2017, 2018; Atahan et al. 2018).

Based on above findings, the aim of this study is the determination effects of total anthocyanins extracted from various sweet cherry on carbonic anhydrase (CA) I and II enzymes and antioxidant activities. In this report, total anthocyanins were extracted from eleven cherry cultivars ('Stella', '0900 Ziraat', 'Bing', 'Regina', 'Noble', 'Starks Gold', 'Merton Premier', 'Berryessa', 'Churchill', 'Lambert' and 'Mazzard') grown in Turkey. 'Mazzard' (Chmielarz 2009) and 'Starks Gold' (Hayaloglu and Demir 2015) varieties are called as 'Kuş Kirazı' and 'Beyaz Anadolu', respectively, in Turkey. Moreover, CA inhibitory activities and antioxidant properties of these eleven cherry cultivars were evaluated.

Materials and Methods

Materials

The sweet cherry ('Stella', '0900 Ziraat', 'Bing', 'Regina', 'Noble', 'Starks Gold', 'Merton Premier', 'Berryessa', 'Churchill', 'Lambert' and 'Mazzard') samples were analyzed in an appropriate stage of maturity. The samples (0.5 kg) were packed in plastic bags, frozen and kept at -18°C before extraction of anthocyanins.

All chemicals and solvents used in analysis were obtained from Sigma Aldrich (Sternheim, Germany), Alfa Aesar (Karlsruhe, Germany) and Merck (Darmstadt, Germany).

Extraction of Total Anthocyanins

Seeds of deep-frozen cherry samples were separated by hand. Cherry samples (about 100 g) were blended twice with 250 mL of methanol acidified with 1.0 N HCl (85:15, v/v) for 2 min in a Waring blender (Waring, Conn, USA). Extract was filtered under vacuum on a Buchner funnel using Whatman No. 1 paper (Whatman Inc., Clifton, N.J.). Filtrate was concentrated to a small volume at 40 °C using Heidolph rotary evaporator (HEI-VAP Value G1, Schwabach, Germany) under vacuum for purification of total anthocyanins. Total anthocyanins were extracted from all sweet cherry cultivars three times and the mean value was calculated.

Purification and Measurement of Total Anthocyanins

The anthocyanins were purified according to the methodology of Zhang et al. (2004). The filtrate containing sugars, organic acids, polyphenolics, and anthocyanins etc. were loaded onto an Amberlite XAD-7 (Alfa Aesar Co., Karlsruhe, Germany) resin column. Firstly, it was washed with distilled water (about 1000 mL) to remove sugars, acids and other water-soluble compounds and then washed with ethyl acetate (about 500 mL) to remove polyphenolics com-

Table 1 Average amounts and maximum absorbances (λ_{max}) of total anthocyanins in sweet cherry cultivars

Sample No	*Sweet cherry cultivars*	*Total anthocyanin amount (mg/100 g, average)*	λ_{max} *(nm)*
N1	Stella	150	283.0, 532.5
N2	0900 Ziraat	98	281.5, 520.0
N3	Bing	102	284.5, 528.5
N4	Regina	305	280.5, 528.5
N5	Noble	219	285.0, 529.0
N6	Starks Gold	141	286.5, 529.5
N7	Merton Premier	58	288.0, 522.5
N8	Berryessa	45	281.5, 528.0
N9	Churchill	70	282.5, 531.0
N10	Lambert	179	283.0, 529.5
N11	Mazzard	168	282.5, 530.5

Table 2 Inhibitory effect on hCA I and hCA II (IC_{50} values) and DPPH activity of total anthocyanins in sweet cherry cultivars

Sample No	*Sweet cherry cultivars*	IC_{50} *(μg/mL)*		*DPPH activity (%)*
		hCA I	*hCA II*	
N1	Stella	4.59	3.02	7.859
N2	0900 Ziraat	2.08	2.55	50.674
N3	Bing	3.55	4.05	58.982
N4	Regina	1.74	4.36	19.611
N5	Noble	5.8	5.94	28.368
N6	Starks Gold	7.3	7. 2	67.365
N7	Merton Premier	0.83	1.16	73.503
N8	Berryessa	3.23	3.06	19.611
N9	Churchill	0.88	3.14	74.102
N10	Lambert	3.39	7.12	58.159
N11	Mazzard	2.91	4.24	35.778

pounds. Finally, total anthocyanins were recovered with methanol containing 0.1% trifluoroacetic acid (v/v). This acidified methanol fraction was combined and evaporated under vacuum to dryness and weighed on GX-300 balance (A&D Co., Tokyo, Japan). 20 mg of total anthocyanins was dissolved with 0.1% TFA-MeOH (v/v) and submitted to spectrophotometric analysis (200–600 nm) using a Shimadzu UV–Vis spectrophotometer (Kyoto, Japan). All measurements were taken in duplicate.

Preparation and Purification of Hemolysate from Blood Red Cells

Blood samples (25 mL) were taken from healthy human volunteers. They were anticoagulated with acid-citrate-dextrose, centrifuged at 2000 g for 20 min at 4 °C and the supernatant was removed. The packed erythrocytes were washed three times with 0.9% NaCl and then haemolysed in cold water. The ghosts and any intact cells were removed by centrifugation at 2000 g for 25 min at 4 °C, and the pH of the haemolysate was adjusted to pH 8.5 with solid Tris-base. The 25 mL haemolysate was applied to an affinity column containing L-tyrosine-sulfonamide-Sepharose-4B (Arslan et al. 1996) equilibrated with 25 mM Tris–HCl/0.1M Na_2SO_4 (pH 8.5). The affinity gel was washed with 50 mL of 25 mM Tris–HCl/22 mM Na_2SO_4 (pH 8.5). The human CA (hCA) isozymes were then eluted with 0.1 M NaCl/25 mM Na_2HPO_4 (pH 6.3) and 0.1 M CH_3COONa/0.5 M $NaClO_4$ (pH 5.6), which recovered hCA-I and hCA-II respectively. Fractions of 3 mL were collected and their absorbance measured at 280 nm.

CA Enzyme Assay

CA activity was measured by the Maren method which is based on determination of the time required for the pH to decrease from 10.0 to 7.4 due to CO_2 hydration (Maren 1960). The assay solution was 0.5 M Na_2CO_3/0.1 M $NaHCO_3$ (pH 10.0), and Phenol Red was added as the pH indicator. CO_2-hydratase activity (enzyme units (EU)) was calculated by using the equation t_0-tc/tc where t_0 and tc are the times for pH change of the nonenzymatic and the enzymatic reactions, respectively.

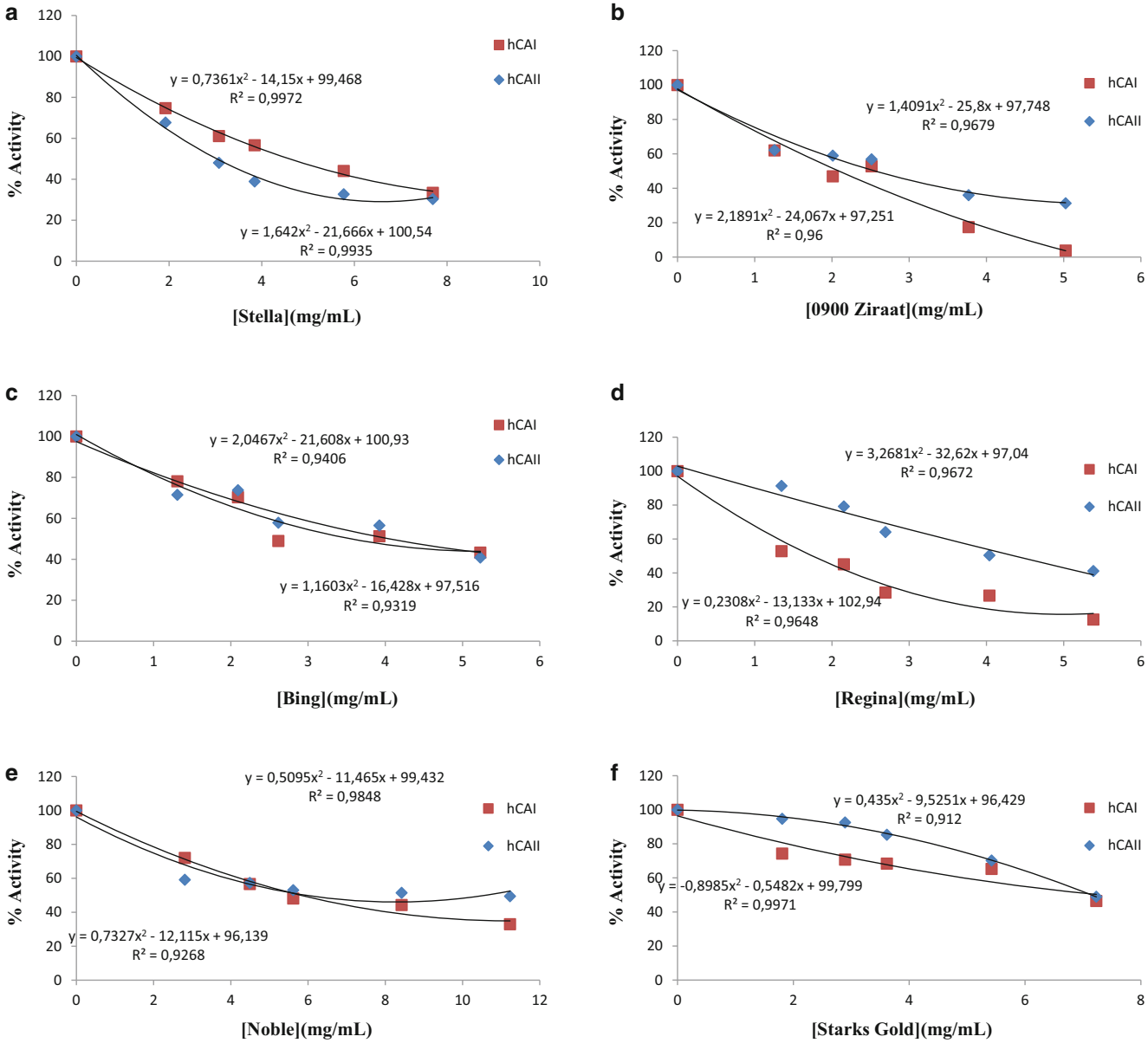

Fig. 1 IC_{50} graphs of total anthocyanins on hCA I and II. **a** Stella, **b** 0900 Ziraat, **c** Bing, **d** Regina, **e** Noble, **f** Starks Gold, **g** Merton Premier, **h** Berryessa, **i** Churchill, **j** Lambert, **k** Mazzard

In Vitro Inhibition Studies

For the inhibition studies of all extracted total anthocyanins, different concentrations of these extracts were added to the enzyme. Activity percentage values of CA for different concentrations of each extract were determined by regression analysis using Microsoft Office 2000 Excel. CA enzyme activity without an extract solution was accepted as 100% activity.

DPPH Assay

Free radical scavenging activities are determined using 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical (Kedare and Singh 2011). 1000 µM stock solutions of the materials were prepared. 2, 5, 10 and 20 µL of these stock solutions were taken and completed to 40 µL with ethanol and then 160 µL of 0.1 mM DPPH solution was added. The absorbance values of the prepared solutions were measured at 517 nm after 30 min of incubation in the dark at room temperature. DPPH activities (%) of the samples were calculated from the obtained absorbance values.

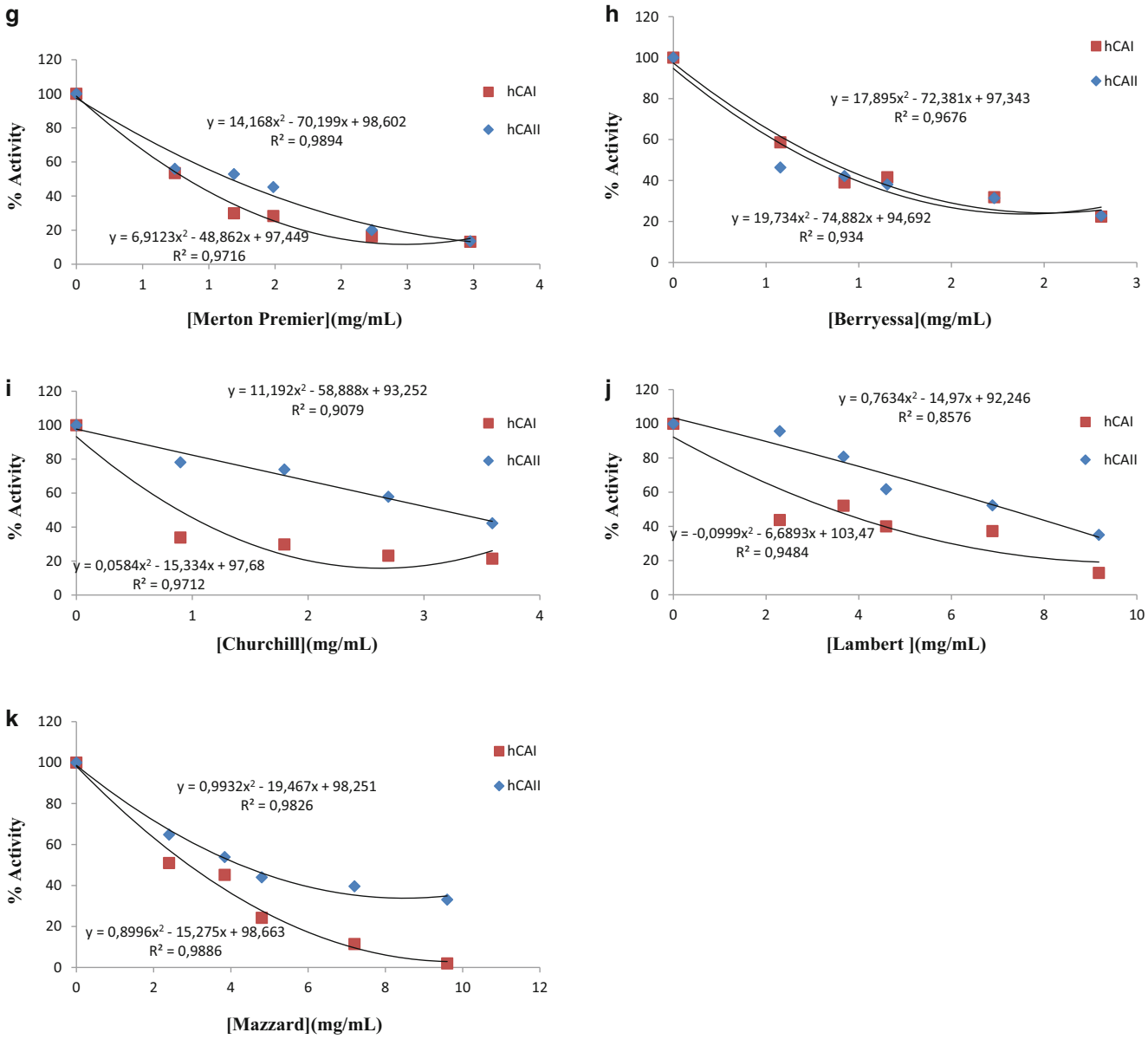

Fig. 1 (continued) IC_{50} graphs of total anthocyanins on hCA I and II. **a** Stella, **b** 0900 Ziraat, **c** Bing, **d** Regina, **e** Noble, **f** Starks Gold, **g** Merton Premier, **h** Berryessa, **i** Churchill, **j** Lambert, **k** Mazzard

Results and Discussion

Average amounts of total anthocyanins from sweet cherry cultivars were between 45 and 305 mg/100 g (Table 1). The highest total anthocyanins amount was in the 'Regina' cultivar (305 mg/100 g), followed by the 'Noble' (219 mg/100 g) and 'Lambert' (179 mg/100 g). The lowest total anthocyanins amount was recorded in the 'Berryessa' cultivar (45 mg/100 g). λ_{max} values and IC_{50} and DPPH activity of total anthocyanins are presented in Table 1 and 2.

IC_{50} graphs were summarized in Fig. 1. All extracted total anthocyanins from sweet cherry cultivars inhibited both hCA I and hCA II enzyme activity. We have determined the IC_{50} values between 0.83–7.30 µg/mL for the inhibition of hCA I and 1.16–7.20 µg/mL for the inhibition of hCA II.

Among all cultivars, 'Merton Premier' was found to be the most active one both hCA I (IC_{50} = 0.83 µg/mL) and hCA II activity (IC_{50} = 1.16 µg/mL) The 'Churchill' (IC_{50} = 0.88 µg/mL) and the 'Regina' (IC_{50} = 1.74 µg/mL) have higher inhibitory activity against hCA I, while the '0900 Ziraat' (IC_{50} = 2.55 µg/mL) and the 'Stella' (IC_{50} = 3.02 µg/mL) have higher inhibitory activity against hCA II. Additionally, most of the cultivars have higher inhibitory activity on hCA I than hCA II.

It was reported that the polyphenols and flavones, as the natural compounds, extracted from various plants such as

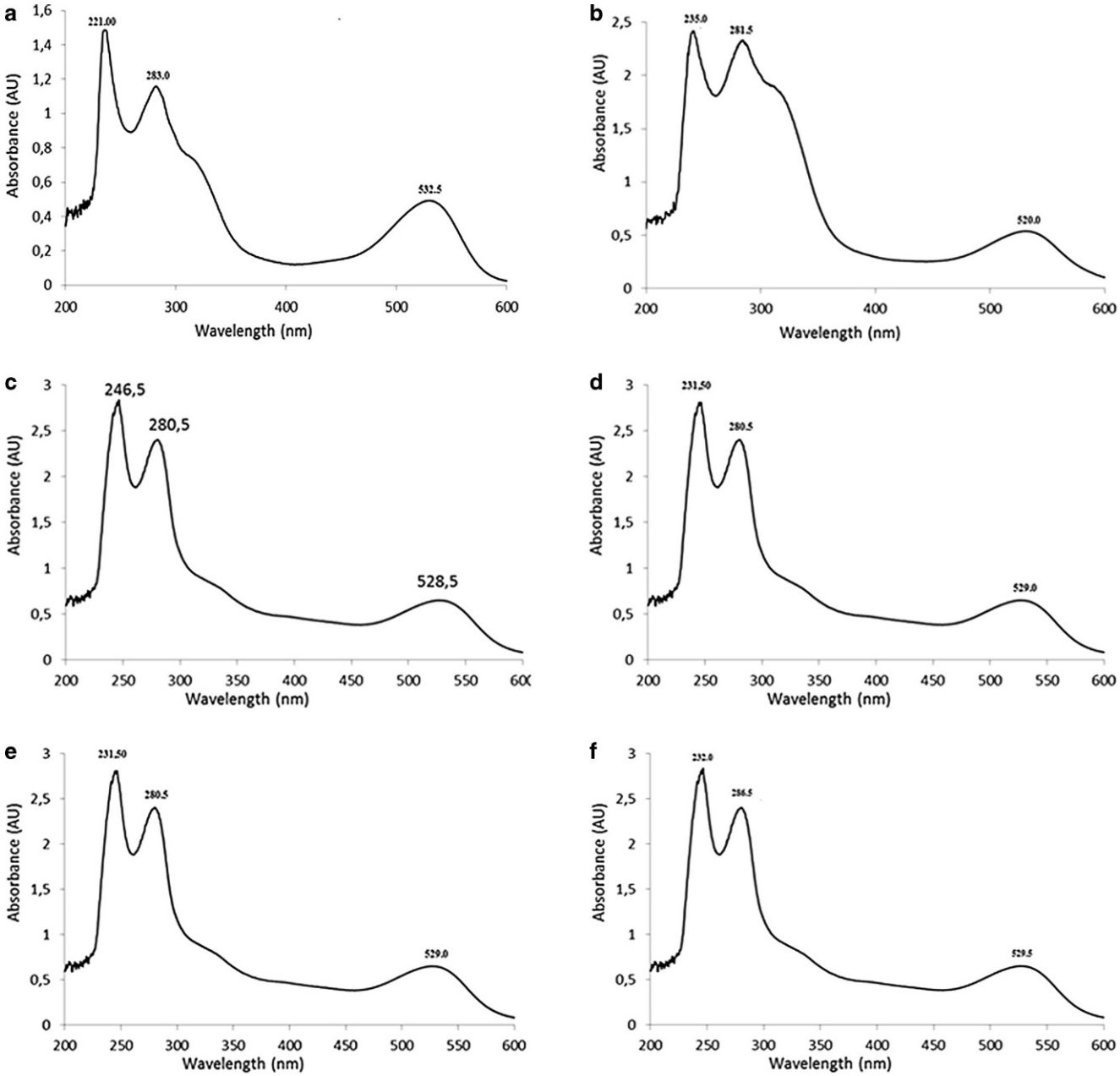

Fig. 2 UV-Vis spectra of total anthocyanins in local sweet cherry cultivars. **a** Stella, **b** 0900 Ziraat, **c** Bing, **d** Regina, **e** Noble, f Starks Gold, **g** Merton Premier, **h** Berryessa, **i** Churchill, **j** Lambert, **k** Mazzard

Morchella esculanta, Padina pavonica, Cystoseria barbata, Black Tea, *Ceramium ciliatum, Ulva rigida, Corallina officinalis* and Linden tree showed CA I and II inhibitory activity. Their minimum concentrations to achieve 50% inhibition for hCA I were 25.52, 27.66, 35.29, 36.66, 44.72, 45.81, 60.02 and 66.50 µg/mL, respectively (Sahin et al. 2012). Although, the extracts obtained from cherries in our study have weak inhibitory effects for hCA I, they have shown inhibitory effects better than some plants.

The differences in total anthocyanins amount and their effects on hCA I and II enzyme activity were determined. We think that these differences are due to the sweet cherry genotypes and genetic variations.

DPPH method is commonly used to measure the ability of antioxidants to sweep free radicals. In this spectrophotometric method, a stable free radical, DPPH (2,2-diphenyl-1-picrylhydrazyl), is used (Kedare and Singh 2011). Antioxidants are based on the ability to degrade the DPPH radical, and when it interacts with radical hydrogen donors, hydrazine is reduced. According to this method, compounds must have strong hydrogen donor groups to exhibit good antioxidant properties. The DPPH activities of the

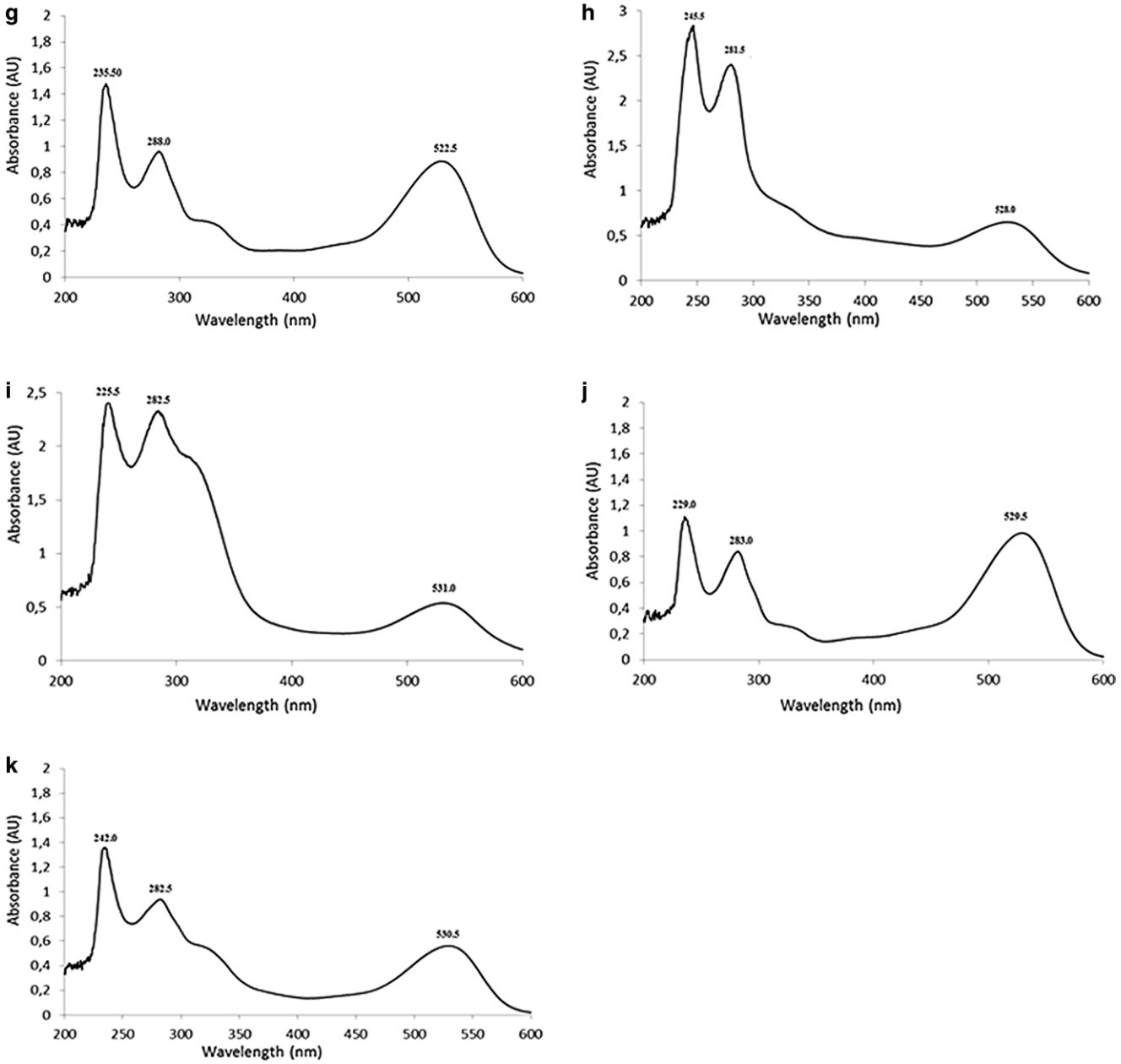

Fig. 2 (continued) UV-Vis spectra of total anthocyanins in local sweet cherry cultivars. **a** Stella, **b** 0900 Ziraat, **c** Bing, **d** Regina, **e** Noble, f Starks Gold, **g** Merton Premier, **h** Berryessa, **i** Churchill, **j** Lambert, **k** Mazzard

extracts were between 7.859% and 74.102% (Table 2). Among them, 'Churchill', 'Merton Premier' and 'Starks Gold' exhibited high antioxidant activity with 74.102%, 73.503% and 67.365%, respectively.

The UV-Visible absorption spectra of total anthocyanins in sweet cherry cultivars were recorded between 200 and 600 nm (Fig. 2). The spectrophotometric analysis of extracts obtained from these cultivars showed maximum absorption bands around 280 nm and 528 nm. Anthocyanins display two distinct absorption bands, one in the UV-region (260–280 nm) and another in the visible region (490–550 nm) (Simoes et al. 2009). These results provided evidence of the anthocyanic nature of the pigments produced in the sweet cherry cultivars grown in Sakarya, Turkey.

Conclusions

In conclusion, total anthocyanins were extracted from eleven sweet cherry cultivars ('Stella', '0900 Ziraat', 'Bing', 'Regina', 'Noble', 'Starks Gold', 'Merton Pre-

mier', 'Berryessa', 'Churchill', 'Lambert' and 'Mazzard') grown in Sakarya, Turkey. Their hCA I and hCA II inhibition and DPPH% activities were examined. 'Regina' (305 mg/100 g) has the highest total anthocyanins amounts, whereas 'Berryessa' (45 mg/100 g) was the lowest total anthocyanins amounts among all cultivars. All total anthocyanins obtained from sweet cherry cultivars inhibited the carbonic anhydrase I and II enzyme activities. Additionally, most of the cultivars have higher inhibitory activity on hCA I than hCA II. 'Merton Premier' (IC_{50} = 0.83 µg/mL and IC_{50} = 1.16 µg/mL, for hCA I and hCA II, respectively) was found to be the best inhibitor in this study. Moreover, 'Churchill' and 'Merton Premier' have high antioxidant activity with 74.102% and 73.503% DPPH activity, respectively. These sweet cherry cultivars could be used as a natural hCA I and hCA II enzyme inhibitors and antioxidant agents.

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Conflict of interest F. Sonmez, Z. Gunesli, T. Demir, K. Cıkrıkcı, A. Ergun, N. Gencer and O. Arslan declare that they have no competing interests.

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