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The metabolites and native Prangos heyniae (H. Duman & M. F. Watson) and their The metabolites and antiityrosinase activity

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ABSTRACT

Purpose and Background: Coumarins are plentiful in Prangos Lindl. (Apiaceae). Previously, along with n-hexane(HEX), chloroform(CHCl3), and methanol(MeOH) extracts, 8 molecules named osthol(1), isoimperatorin(2), oxypeucedanin(3), 7-methoxy-isoarnottinin-4'-O-β-ᴅ-glucopyranoside(4), 7-methoxy-isoarnottinin-4'-O-rutinoside(5), oxypeucedanin hydrate-3'-O-β-ᴅ-glucopyranoside(6), 1-methylethyl-6-O-D-apio-β-ᴅ-furanosyl-β-ᴅ-glucopyranoside(7), and cnidioside A(8) were obtained from the roots of endemic Prangos heyniae H. Duman & M. F. Watson. New compounds were identified as 4 and 5. The neuroprotective effects of coumarins are well-documented. In neurodegenerative illnesses like Parkinson's and Alzheimer's disease (AD), the tyrosinase and cholinesterase enzymes, respectively, are crucial to the progression of the disease. Thus, our objective was to assess the anticholinesterase and antityrosinase activities of the root extracts and compounds 1–8 of Prangos heyniae.

Methods: The spectrophotometric evaluation of the samples indicated that they inhibited tyrosinase and acetylcholinesterase-butyrylcholinesterase (AChE-BChE). The samples were screened at a concentration of 1000 µg/mL. The IC50 values were determined by linear regression analysis and presented as the results of triplicate studies of the samples. As positive controls, antityrosinase and anticholinesterase investigations, respectively, made use of kojic acid and galantamine. The result is that the antityrosinase activity was seen only in the MeOH extract, with an IC50 value of 543.37±7.45 µg/mL. The inhibitory actions of AChE and BChE were shown by the CHCl3 extract, with IC50 values of 273.92 ± 32.07 and 38.68±2.56 µg/mL, respectively. Out of the substances that were evaluated, six exhibited moderate BChE-specific inhibitory action (IC50= 91.93±3.86µg/mL), which was forty times weaker than galantamine (IC50= 2.25 ± 0.05µg/mL).

The results showed that the CHCl3 extract effectively inhibited BChE activity. Based on these results, Prangos heyniae may be a good candidate for future research into Alzheimer's disease as a natural source for the creation of new BChE inhibitors.

Prangos heyniae, coumarin, oxypeucedanin hydrate-3'-O-β-ᴅ-glucopyranoside, anticholinesterase activity, and antityrosinase activity are all terms that pertain to this compound.

INTRODUCTION

There are 45 species of the Prangos Lindl. (Apiaceae) genus, which is an element of Iran and Turan (Lyskov, Degtjareva, Samigullin, & Pimenov, 2017). The species is distributed from Europe to Tibet, with the majority of its plants found in Iran and Turkey (Lyskov et al., 2017; Menemen, 2012; Mottaghipisheh, Kiss, Tóth, & Csupor, 2020). Aytaç & Duman (2016), B. Başer & Pehlivan (2015), Lyskov et al. (2017), Menemen (2012), and Mottaghipisheh et al. (2020) all state that species in the genus thrive on calcareous rocks, basalt rocky soils, saline soils, and mountain slopes. Behçet, Yapar, and Olgun (2019), Aytaç and Duman (2016), and Menemen (2012) count nineteen taxa, eleven of which are unique to Turkey. There are a number of documented traditional uses for plants belonging to this genus. According to Bulut, Tuzlacı, Doğan, and Şenkardes (2014), the plant's aerial parts are used as a stimulant and carminative, while the roots have medicinal uses as an antihemorrhoidal, wound-healing, and aphrodisiac in Anatolian traditional medicine. Previous research by Farooq et al. (2014), Kogure et al. (2004), Massumi, Fazeli, Alavi, & Ajani (2007), Özek et al. (2007), Ulubelen et al. (1995), and Zahri, Razavi, Niri, &

Mohammadi (2009) has generally linked bioactivity studies to the antibacterial, cytotoxic, and antioxidant properties of Prangos species. In addition, prior research has documented studies on its anti-inflammatory, wound healing, antiviral, hepatoprotective, antidiabetic, and vascular reactivity effects (Doković et al., 2004; Farkhad, Farokhi, & Tukmacki, 2012; Farokhi, Farkhad, & Togmechi, 2012; Sevin et al., 2022; Shokoohinia, Sajjadi, Gholamzadeh, Fattahi, & Behbahani, 2014; Tada et al., 2002; Zahri et al., 2009). Albayrak, Demir, Koyu, & Baykan (2022); Dalll'Acqua et al. (2022); Mottaghipisheh et al. (2020); Zengin et al. (2022) are among the publications that have examined the antiicholinesterase activities of numerous Prangos species, among other bioactivity investigations of the genus. The unique species Prangos heyniae, which is known as "Bozçakşır" in Anatolia, is a perennial plant that may be found in the province of Konya in Turkey (Duman & Watson, 1999; Menemen, 2012). This indigenous plant has not been the subject of many published investigations. Research on the bioactivity of P. heyniae has shown that it has antioxidant, mosquitocidal, and anticandidal properties (Ahmed, Güvenç, Küçükboyacı, Baldemir, & Coşkun, 2011; Öke-Altuntaş, Aslım, Duman, Gülpınar, & Kartal, 2015; Özek et al., 2018). A number of studies have examined the plant's essential oil composition in its fruits and roots and identified elemol, α-pinene, kessane, and germacrene D as the main compounds (K. H. C. Başer, Özek, Demirci, & Duman, 2000; Karahisar, Köse, İşcan, Kürkçüoğlu, & Tugay, 2022; Özek et al., 2018; Zengin et al., 2022). Özek et al. (2018) also reported that the essential oils of P. heyniae fruits may be extracted using preparative gas chromatography to produce a sesquiterpene ketone called 3,7(11)-eudesmadien-2-one. Various investigations have assessed the antiityrosinase and anticholinesterase activity of essential oils and extracts derived from the aerial portions of P. heyniae (Dall'Acqua et al., 2022; Zengin et al., 2022). But no one has ever looked into the plant's roots for anticholinesterase and antityrosinase capabilities, as far as we know. The coumarins and furanocoumarins are the most abundant metabolites in the genus Prangos. Studies on neurodegenerative diseases have shown that these compounds inhibit the enzymes acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) (De Souza, Renn O. B., & Figueroa-Villar, 2016; Mottaghipisheh et al., 2020). When the body produces too much melanin, a condition known as hyperpigmentation, it is because tyrosinase is involved in the process. Dopamine neurotoxicity causes Parkinson's disease; elevated amounts of neuromelanin, a kind of melanin pigment, have been linked to this condition. Chang (2009), Fais et al. (2009), Shu et al. (2020), and Zolghadri et al. (2019) are among the research that have examined the tyrosinase inhibitory activity of these metabolites, which is a significant target for decreasing melanocyte function. Among these compounds, osthole, oxypeucedanin, oxypeucedanin hydrate, psoralen, xanthotoxin, marmesin, heraclenin, heraclenol, imperatorin, and isoimperatorin stand out as the primary coumarins and furanocoumarins found in Prangos species (Abbas-Mohammadi et al., 2018; Bruno et al., 2021; Mottaghipisheh et al., 2020; Zengin et al., 2020). The hunt for a cure for neurological illness has recently put coumarins and furanocoumarins at the forefront. Research on the cholinergic route (Karakaya et al., 2020; Orhan et al., 2021) and anti-amyloidogenic action (Palmioli et al., 2019) is providing more and more evidence for the neuroprotective effects of coumarin and furanocoumarin derivatives, as are research investigating their metabolic pathways. Considering this information, the aim of this study was to evaluate the in vitro anticholinesterase and antityrosinase potential of HEX, CHCl3, and MeOH extracts of the plant roots along with the compounds [Figure 1; osthol (1), isoimperatorin (2), oxypeucedanin (3), 7-methoxy isoarnottinin 4'-O-β-D-glucopyranoside (4), 7-methoxy isoarnottinin 4'-O-rutinoside (5), oxypeucedanin hydrate-3'-O-β-D- glucopyranoside (6), 1-methylethyl 6-O-D-apio-β-D-furanosyl-β- D-glucopyranoside (7), and cnidioside A (8)] obtained from our previous study (Albayrak, Demir, Kose, & Baykan, 2021). We aim to uncover the neuroprotective and anti-hyperpigmentation potential of this Turkish endemic plant and its chemical components in order to develop novel candidate metabolites for the prevention and treatment of neurodegenerative and hyperpigmentation disorders. In summary, we hope to reveal the pharmacological value of this plant.

MATERIALS AND METHODS

Prof. Dr. Serdar Gokhan Senol of Ege University's Department of Biology and Faculty of Science identified plant extracts and extracted chemicals of Pungos heyniae H. Duman & M. F. Watson, which were gathered in Konya province in 2016.

Izmir, Turkey's Herbarium at Ege University's Faculty of Pharmacy has a voucher specimen (IZEF-6051). The roots of the plants that had been air-dried were previously extracted using HEX, CHCl3, and MeOH in that order. In

addition, the extracts were subjected to chromatographic procedures in order to extract eight chemicals, including six coumarin derivatives (1-6), one isopropyl glycoside (7), and one benzofuran derivative (8), which were then identified using spectroscopic techniques (Albayrak et al., 2021). The HEX, CHCl3, and MeOH extracts and isolated molecules named osthol (1), isoimperatorin (2), oxypeucedanin (3), 7-methoxy isoarnottinin 4'-O-β-D-glucopyranoside (4), 7-methoxy isoarnottinin 4'-O-rutinoside (5), oxypeucedanin hydrate-3'-O-β-D-glucopyranoside (6), 1-methylethyl 6-O-D-apio-β-D-furanosyl- β-D-glucopyranoside (7), and cnidioside A (8) used in this study were isolated from the roots of Prangos heyniae in the above-mentioned work (Albayrak et al., 2021).

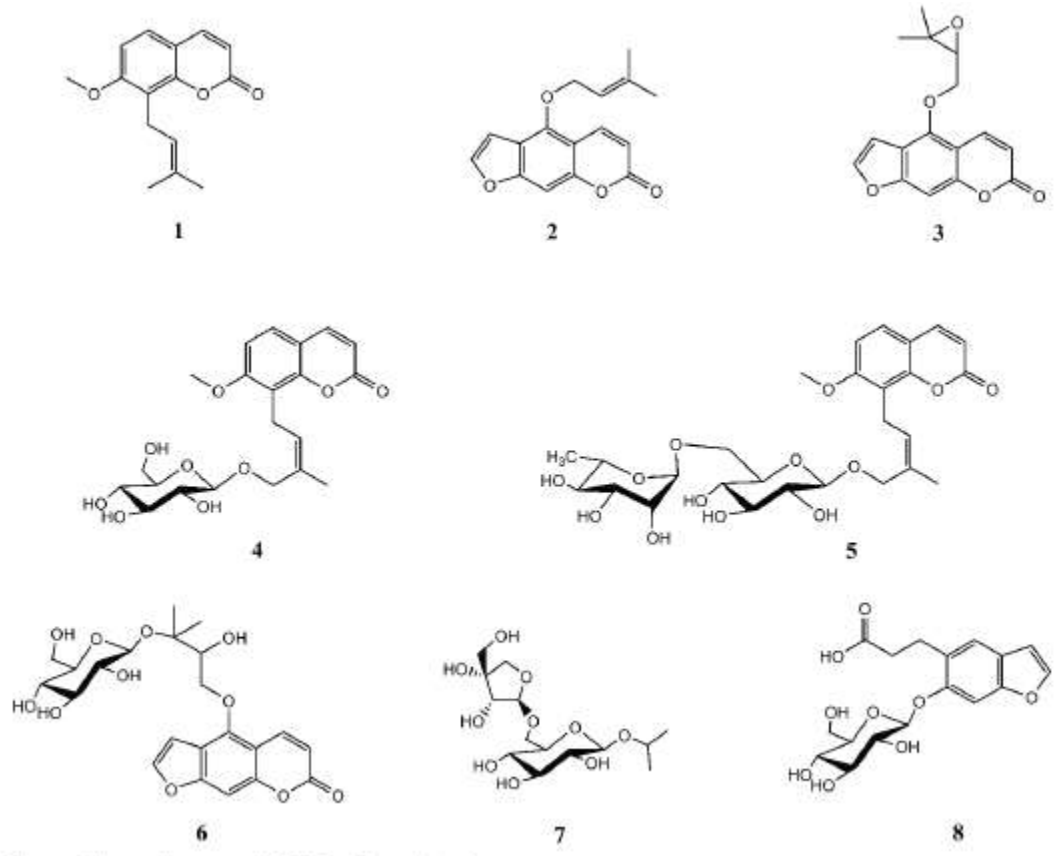

Figure 1. The tested compounds **1-8** from *Prangos heyniae*.

The action against cholinesterase

Using a modified version of Ellman's technique (Ellman, Courtney, Andres, & Featherstone, 1961), the inhibitory activities of AChE and BChE were assessed in the extracts and isolated compounds. Enzymes were sourced from electric eel AChE and horse serum BChE. The substrates for the enzymatic reaction were butyrylthiocholine iodide (3 mM) and acetylthiocholine iodide (3 mM). The anticholinesterase activity was measured using 5, 5'-Dithio-bis 2-nitrobenzoic acid (DTNB). In a 96-well microplate, the following ingredients were added: 150 µL of 0.1 M sodium phosphate buffer, 0.01 M of DTNB, water for sample preparation (DMSO: H2O, 1:9), and acetylcholinesterase/butyrylcholinesterase enzymes at a concentration of 0.1 Unit/mL. The samples were first shaken on an orbital shaker at 300 rpm for 5 minutes at room temperature. After that, 3 mM substrate (in buffer) was added to start the reaction. Using a microplate reader, the kinetic absorbance was measured at 412 nm at room temperature at 30-second intervals over a 10-minute incubation period. The enzyme activity was determined by comparing the absorbance of the buffer without inhibitor to that of the test performed throughout the incubation time

and then linearly changing the two. We used the following formula to determine the cholinesterase inhibition activity data;

$$\% \text{ inhibition} = [(A_{blank} - A_{sample}) / A_{blank}] \times 100$$

This is where the absorbance at 412 nm with the extract/isolated compound/positive control is denoted as Asample and Ablank is the absorbance with sodium phosphate buffer (instead of the tested sample). Galantamine served as the reference medication and positive control. Sigma Plot 12.0 Enzyme Kinetics Module 1.3 was used to determine the inhibitory kinetics of galantamine using the Lineweaver-Burk, Michaelis-Menten, and Eadie-Hofstee techniques (Albayrak et al., 2022). This allowed us to assess the validity of our experimental procedure. The findings from three independent tests were shown using IC50 values, which are the concentrations at which 50% of the enzyme activity is inhibited. These values were determined by linear regression analysis, with an initial test concentration of 1000 µg/mL for the substances that were tested. In order to find their IC50 values, the chosen test samples were examined at concentrations of 1000 µg/mL and 15.625 µg/mL. In order to accurately determine the parameters of the enzyme inhibition test and the findings of the activity research, the methodology was developed and optimized via an inhibition kinetic study using galantamine as a reference medication for ChE inhibition. The kinetics of inhibition were studied using acetylthiocholine iodide as a single substrate at concentrations ranging from 31.25 to 125 µM, galantamine as a single inhibitor at concentrations ranging from 0.0875 to 0.35 µM, and a control group that did not receive any inhibitory treatment (0 µM). The results of the competitive type inhibition test were in agreement with those reported in the galantamine literature therefore validating our research approach (Ellman et al., 1961; Albayrak et al., 2022).

The activity of antityrosinase

To measure the inhibitory activity against tyrosinase, an adjusted 96-well microplate assay was used. The reference medication used was kojic acid. Twenty-five microliters of the samples were combined with one hundred fifty microliters of 2 mM L-dopa in a pH 6.8 phosphate buffer. Two minutes of pre-incubation at 25 °C in darkness followed. The mixture was then incubated at 25 °C for 10 minutes after adding 25 µl of tyrosinase enzyme (50 Unit/mL in phosphate buffer). During the 10-minute reaction period, kinetic measurements were taken at 30-second intervals using a microplate reader (Clariostar, BMG Labtech) set at 475 nm. This allowed us to calculate the linear change in absorbance during dopachrome production. The following formula was used to compute the findings of tyrosinase inhibitory activity;

$$\% \text{ inhibition} = [(A_{blank} - A_{sample}) / A_{blank}] \times 100$$

Ablank represents the absorbance at 475 nm with the sample solvent (a mixture of DMSO and water in a 2:3 ratio), whereas Asample represents the absorbance with the extract or isolated chemical. For the control, kojic acid was used. The IC50 values obtained by linear regression analysis, with an initial test concentration of 1000 µg/mL for the tested materials, were used to show the findings of the triplicate analysis. In order to get the IC50 values, the chosen test samples were examined at concentrations of 1000 µg/mL and 15.625 µg/mL. (Yesil-Celiktas, Koyu, Kazan, Demir, Haznedaroglu, & 2018).

Data analysis using statistical methods

The GraphPad Prism software, version 5.03 (GraphPad Software, San Diego, California, USA), was used to analyze the data. This data was presented as '± standard deviation of the mean'. The findings of the triplicate analysis were presented as the IC50 values of the tested substances. As a result, $p<0.05$ was chosen as the threshold of significance.

RESULTS AND DISCUSSION

The action against cholinesterase

To test for AChE and BChE inhibitory activity, we used HEX, CHCl3, and MeOH extracts of P. heyniae roots, together with 8 pure compounds (Figure 1). The studied extracts' IC50 values are shown in Table 1. The results showed that the compounds and extracts were linear, with R2 values more than 0.9500 and RSD% values lower than 11.71% and 4.2%, respectively. At a concentration of 1000 µg/mL, neither the HEX nor the MeOH extracts exhibited AChE inhibitory action. Nevertheless, the AChE and BChE enzymes were both inhibited by the CH3Cl3 extract, with IC50 values of 273.92 ± 32.07 µg/mL and 38.68 ± 2.56 µg/mL, respectively. Its AChE inhibitory activity was low, while its BChE inhibitory activity was high (17-fold lower than galantamine). Previous research has investigated the anticholinesterase activities of various Prangos species extracts and essential oils in an effort to identify future neuroprotective agents (Abbas-Mohammadi et al., 2018; Bruno et al., 2021; Dall'Acqua et al., 2022; Zengin et al., 2022, 2020). Previous research examined the anticholinesterase activity of HEX, dichloromethane (DCM), and MeOH extracts derived from the aerial portions of P. gaube.

Table 1. Anticholinesterase and antityrosinase activities of *P. heyniae* extracts and compounds 1-8.

	IC_{50} ± S.D. [µg/mL] [a]		
Extracts/ Com-pounds	AChE	BChE	Tyr
HEX	-	-	-
$CHCl_3$	273.92 ± 32.07 (R^2=0.9724)	38.68 ± 2.56 (R^2=0.9717)	-
MeOH	-	-	543.37 ± 7.45 (R^2=0.9654)
1	-	-	-
2	-	-	-
3	-	-	-
4	-	-	-
5	-	-	-
6	-	91.93 ± 3.86 (R^2=0.9959)	-
7	-	-	-
8	-	-	-
Galan-tamine [b]	0.22 ± 0.02 (R^2=0.9571)	2.25 ± 0.05 (R^2=0.9518)	
Kojic acid [c]			3.38 ± 0.17 (R^2=0.9502)

The most effective BChE inhibitor, according to the study by Bahadori, Zengin, Bahadori, Maggi, and Dinparast (2017), was found to be DCM extract, which contained 3.51±0.24 mg GEs/g, galantamine equivalents. The AChE inhibitory activity of HEX (200 µg/mL) and EtOAc (200 µg/mL) extracts from the aerial parts of P. ferulacea was investigated in a separate study by Abbas-Mohammadi et al. (2018). The HEX extract showed an inhibition of 75.6%±2.8% and the EtOAc extract 63.8±1.3%. In both research, coumarins were identified as the primary group responsible for the elevated activity (Abbas-Mohammadi et al., 2018; Bahadori et al., 2017). Zengin et al. (2022) conducted a study on the cholinesterase inhibitory properties of essential oils extracted from various plant parts. Of the samples tested, only the essential oil of P. heyniae (9.85±0.20 mg GALAE/g, galantamine equivalents) demonstrated specific inhibitory activity against BChE. To find out if the aerial portions of P. uechtritzii, P. meliocarpoides var. meliocarpoides, and P. heyniae inhibited cholinesterase, Dall'Acqua et al. tested HEX, EtOAc, MeOH, and water extracts. HEX (galantamine equivalents, AChE=2.39±00.6 mg GALAE/g, BChE=7.83±0.18 mg GALAE/g) and simultaneously The EtOAc extracts of P. heyniae showed inhibitory effects against BChE with concentrations of 1.58±0.38 mg GALAE/g and 7.64±0.15 mg GALAE/g, respectively, in the galantamine equivalents. It was found that the action was caused by chemicals called coumarins and hydrolyzable tannins (Dall'Acqua et al., 2022). In light of our findings and previous research with Prangos species on cholinesterase inhibition, P. heyniae may be a promising source for neurotherapeutic medicines, particularly BChE inhibitor drugs. With an IC50 value of 91.93 ± 3.86 µg/mL, 6 out of the isolated compounds that were evaluated exhibited BChE inhibitory action. With an IC50 value of 2.25 ± 0.05 µg/mL, it showed 40 times less activity than galantamine. The inhibition of AChE was not seen at 1000 µg/mL, however. The aglycone group of 6—oxypeucedaninhydrate—has been shown to be ineffective against AChE and BChE enzymes in vitro in prior research (Albayrak et al., 2022; Orhan et al., 2021; Youkwan, Sutthivaiyakit, & Sutthivaiyakit, 2010). If the glucose moiety is present and positioned at C-3', it may explain why 6 has a stronger impact on BChE than its aglycone. Research into Alzheimer's disease has shown that AChE, rather than BChE, regulates acetylcholine levels in both healthy brains and those in the early stages of the disease. Around the middle to end of the illness, acetylcholine levels drop in AChE activity while BChE levels keep going up (Greig, Lahiri, & Sambamurti, 2002; Greig et al., 2001). According to Walsh, Rockwood, Martin, and Darvesh (2011), BChE may play a key role in the decline of acetylcholine levels in AD. That is why blocking BChE is just as crucial as blocking AChE. Coumarins and furanocoumarins have shown selectivity for BChE in several experiments (De Souza et al., 2016). In particular, our results for the BChE inhibitory effect of oxypeucedanin hydrate-3'-O-β-□-glucopyranoside (6) are in agreement with previous studies that found that the presence of the prenyl moiety at the C-8 position (Granica et al., 2013; Wszelaki, Paradowska, Jamróz, Granica, & Kiss, 2011) and the furan ring at the C-6 position (Özbek et al., 2018; So & Young, 2007) were associated with an increase in the BChE inhibitory activity of coumarins and furanocoumarins. The inhibitory effect against AChE and BChE was not seen in the other drugs at 1000 µg/mL.

Isolated compounds 1–8 have less inhibitory effects against AChE and BChE than does CHCl3 extract. Compared to galantamine (IC50=2.25±0.05 µg/mL), the extract showed a 2.4-fold lower activity in the BChE inhibition assay. Compound 6, on the other hand, showed a 40-fold lower activity than the reference (IC50=91.93±3.86 µg/mL). The higher activity of the extract can be because of the synergistic action of all the molecules or because of additional active chemicals that are not separated.

To understand how the extract and chemicals work, however, further research is required.

The activity of antityrosinase

Testing for antityrosinase activity was conducted on all three extracts in addition to the pure chemicals shown in Figure 1. All of the analyzed extracts' IC50 values are shown in Table 1. R2 values greater than 0.9500 and relative standard deviation percentages lower than 1.37% were used to establish linearity for all samples that were examined. An IC50 value of 543.37 ± 7.45 µg/mL was observed for tyrosinase inhibition by just the MeOH extract. Compared to the reference medication, kojic acid, the extract's activity was 160 times lower (IC50= 3.38 ±0.17 µg/mL). At a concentration of 1000 µg/mL, the enzyme was unaffected by compounds 1-8. Studies including Prangos species that have investigated their ability to suppress tyrosinase are few (Bahadori et al., 2017; Dall'Acqua et al., 2022; Orhan et al., 2021; Zengin et al., 2022, 2020). In a recent study, Zengin et al. looked at the tyrosinase inhibitory properties of

essential oils extracted from three different plant parts: P. uechtritzii, P. meliocarpoides var. meliocarpoides, and P. heyniae. The results showed that the essential oils of P. meliocarpoides var. meliocarpoides had the strongest inhibitory activity, with 69.56±4.80 mg KAE/g of kojic acid equivalents.

The research found that P. heyniae had considerable antityrosinase activity, with 53.91±2.11 mg KAE/g, kojic acid equivalents (Zengin et al., 2022). The tyrosinase inhibitory properties of various extracts from the aerial parts of P. uechtritzii, P. meliocarpoides var. meliocarpoides, and P. heyniae were studied by Dall'Acqua et al. The study found that the HEX extract of P. meliocarpoides var. meliocarpoides had the strongest activity, with 81.15±0.19 mg KAE/g, kojic acid equivalents. P. heyniae was the least active of the three species in the same research. According to our research (Dall'Acqua et al., 2022), the MeOH extract of P. heyniae had the highest antiityrosinase activity compared to the other extracts, with 65.20±0.89 mg KAE/g, kojic acid equivalents. The presence of polar chemicals in the plant, including tannins and glycosylated coumarins, is responsible for this. No anti-tyrosinase action was shown at 100 µg/mL in a different investigation that examined 17 coumarin derivatives, including osthol, isoimperatorin, oxypeucedanin, and oxypeucedanin hydrate (the aglycone unit of compound 6). (Orhan et al., 2021). Previous investigations have shown that coumarins and Prangos species have mild to moderate antityrosinase action. Our results align with these findings (Dall'Acqua et al., 2022; Erdogan Orhan, Orhan, & Gurkas, 2011; Shu et al., 2020; Zengin et al., 2022).

CONCLUSION

In conclusion, HEX, CHCl3, and MeOH extracts of the roots of endemic P. heyniae and the isolated metabolites; 7-methoxy isoarnottinin 4'-O-β-D-glucopyranoside (4), 7-methoxy isoarnottinin 4'-O-rutinoside (5), oxypeucedanin hydrate-3'-O-β-D- glucopyranoside (6), 1-methylethyl 6-O-D-apio-β-D-furanosyl- β-D-glucopyranoside (7), and cnidioside A (8) were evaluated for antityrosinase and anticholinesterase activities for the first time in this study. There was a specific inhibition of BChE activity by the chloroform extract. Additional investigation into its potential as a natural source for the creation of new BChE inhibitor medications for the treatment of Alzheimer's disease is warranted. The effects of the extracts' activities are attributed to coumarins and furanocoumarins, which are considered active principles.

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