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α-Amylase and α-glucosidase inhibitory activities of the extracts and constituents of *Ferulago blancheana, F. pachyloba* and *F. trachycarpa* roots

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Abstract

Eleven coumarins named osthole (**1**), imperatorin (**2**), bergapten (**3**), prantschimgin (**4**), grandivitinol (**5**), suberosin (**6**), xanthotoxin (**7**), felamidin (**8**), marmesin (**9**), umbelliferone (**10**), ulopterol (**11**), and a sterol mixture consisted of stigmasterol (**12**), β-sitosterol (**13**) were isolated from the roots of *Ferulago blancheana, F. pachyloba* and *F. trachycarpa* through *in vitro* bioassay-guided fractionation processes. The extracts and bioactive compounds were evaluated for their *a*-amylase and *a*-glucosidase activities. Among the tested compounds, felamidin and suberosin showed significant *a*-glucosidase inhibitory activity with IC_{50} values of 0.4 and 0.9 mg/mL, respectively, when compared to the reference standard acarbose (IC_{50} = 4.9 mg/mL). Grandivitinol (IC_{50} = 20.0 mg/mL) had the lowest inhibitory effect. On the other hand, none of the tested extracts were found to be active on *a*-amylase inhibition. This is the first report on isolation, characterization of the bioactive compounds and evaluation the *a*-amylase and *a*-glucosidase inhibitory activities of these species.

Introduction

Ferulago W. Koch. is a perennial genus of Apiaceae and is represented by approximately 50 taxa throughout the world and 35 taxa (18 of them are endemics) in Turkey. Hence Anatolia is considered as the gene center of this genus (Güner et al., 2012). *F. blancheana* Post ex Boiss. and *F. pachyloba* (Fenzl) Boiss. are endemic perennial species, growing only in Niğde-Central Anatolia and Kayseri-Central Anatolia, Turkey respectively, however *F. trachycarpa* Boiss. is not an endemic species, growing in Antalya-Southeastern Anatolia, Turkey (Peşmen, 1972; Troia et al., 2012)

Ferulago species have been used in folk medicine as digestive, carminative, tonic, sedative, vermifuge and aphrodisiac. It is also used to relieve headache, ulcers, hemorrhoids, snake bites, and spleen diseases. *Ferulago* species are used as salad or spice and food for goats and deers (Erdurak, 2003).

Coumarins, indicated as the common metabolites of *Ferulago* species (Erdurak, 2003), have various biological activities such as antihyperglycemic (Tchamadeu et al., 2010), antidiabetic (Patel et al., 2012), anti-hypertensive (Gantimur et al., 1986), antiadipogenic (Shin et al., 2010), anticoagulant, anti-inflammatory, antibacterial,

antifungal, antiviral (Venugopala et al., 2013), anti-tubercular (Chiang et al., 2010), anti-cancer (Luo et al., 2011), anti-oxidant (Basile et el., 2009), anti-convulsant (Luszczki et al., 2009) and neuroprotective (Wang et al., 2012).

Coumarins may be a potential source of new anti-diabetic agents and may also be useful for peripheral tissues by improving the insulin resistance and the increasing glucose uptake (Zhang et al., 2017). Peucedanol 7-O-β-D-glucopyranoside (Lee et al., 2004), coumarin (1,2-benzopyrone) (Pari and Rajarajeswari, 2009), umbelliferone (Ramesh and Pugalendi, 2005), imperatorin, psoralen, 5-methoxypsoralen, 8-methoxy-psoralen, iso-oxypeucedanin, pabulenol, oxypeucedanin methanolate, oxypeucedanin hydrate (Shalaby et al., 2014), iso-bergapten, pimpinellin, isopimpinellin, sphondin, scopoletin, phellopterin, byakangelicin and daucosterol (Zhang et al., 2017) were isolated from various plants belonging to the Apiaceae family and they were found to be antidiabetic. So, it may be a good approach in the treatment of type 2 diabetes.

This is the first report of the isolation and structure elucidation study on the roots of *F. blancheana, F. pachyloba* and *F. trachycarpa* to afford 11 coumarins (**1-11**) and a sterol mixture (**12-13**). The *a*-amylase and *a*-glucosidase inhibitory activities of the isolated coumarins were also evaluated.

Materials and Methods

General experimental procedures

NMR spectra were recorded on a Varian Mercury Plus at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR by using TMS as the internal standard. The solvents were $CDCl_3$. ESI-MS was performed on Waters Micromass ZQ mass spectrometer. Column chromatographies were performed on silica gel 60 (0.063-0.200 mm, Merck) and sephadex LH-20 (Fluka). Thin layer chromatography (TLC) was carried out on pre-coated Kieselgel 60 F_{254} aluminum sheets (Merck).

Plant material

Flowering plants of *F. blancheana, F. pachyloba* and *F. trachycarpa* were collected in 2014 from the Antalya, Niğde and Kayseri (Turkey), respectively and identified by one of the authors (Hayri Duman). The voucher specimens were kept in the Herbarium of Ankara University, Faculty of Pharmacy (Herbarium numbers: AEF 26677, AEF 26674 and AEF26673, respectively).

Extraction and isolation

Air-dried roots of *F. blancheana* (750 g), *F. pachyloba* (600 g) and *F. trachycarpa* (450 g) were powdered and macerated three times with methanol for 8 hours in a water bath not exceeding 45°C (4 × 2 L) using a mechanical mixer at 300 rpm. The combined extracts were filtered and concentrated till dryness, then dispersed in methanol-water (1:9) and fractionated four times with 400 mL of dichloromethane, ethyl acetate and *n*-butanol, respectively. The same extraction and fractionation procedure were applied for the aerial parts of the plants. On the other hand, 50 g of roots and aerial parts were grounded and macerated with 500 mL of distilled water for 8 hours/3 days at 30 to 35°C. The amounts of the powdered plants and obtained extracts are shown in Table I.

As a result of the bioguided fractionation study, the effective dichloromethane extracts of the roots of all species were first submitted to a silica gel column and eluted with a gradient of *n*-hexane:ethyl acetate (100:0 → 0:100, v/v) and ethyl acetate:methanol (100:0 → 0:100, v/v), and nine fractions (Fr. A-I) were obtained. Fr. A was subjected to a silica gel column which was eluted with a mixture of *n*-hexane:ethyl acetate (95:5) and compounds **12** and **13** were obtained as a mixture (217 mg). Repetitive silica gel column chromatography with *n*-hexane-ethyl acetate (90:10 and 95:5) solvent system on Fr. B gave the compound **1** (220 mg). Fr. C was applied to the silica gel column eluting with *n*-hexane:ethyl acetate (85:15) and sephadex LH-20 column eluting with ethyl acetate to give the compounds **2** (125 mg) and compound **3** (130 mg). Eluting with *n*-hexane-ethyl acetate (90:10) over silica gel column of Fr. D gave the compound **4** (400 mg) and Fr. E gave the compounds **5** (150 mg) and compound **6** (330 mg). Fr. F eluted with 25% ethyl acetate in *n*-hexane and rechromatographed with 25% ethyl acetate in *n*-hexane on the silica gel column to obtain compound **7** (110 mg).

Table I

Amounts of the powdered plants and obtained extracts

Species	Used parts	Powdered (g)	MeOH (g)	CH_2Cl_2 (g)	EtOAc (g)	BuOH (g)	Aqueous residue (g)	Lyophilized (g)
F. blancheana	Root	750	86.6	28.5	2.3	12.2	23.4	5.8
	Aerial part	50	3.2	1.9	0.5	0.6	0.4	1.8
F. pachyloba	Root	600	83.3	23.6	1.5	13.1	21.3	5.0
	Aerial part	50	3.3	1.8	0.5	0.6	0.5	2.0
F. trachycarpa	Root	450	86.8	26.3	2.4	13.5	22.1	4.8
	Aerial part	50	3.4	1.7	0.5	0.6	0.6	1.7

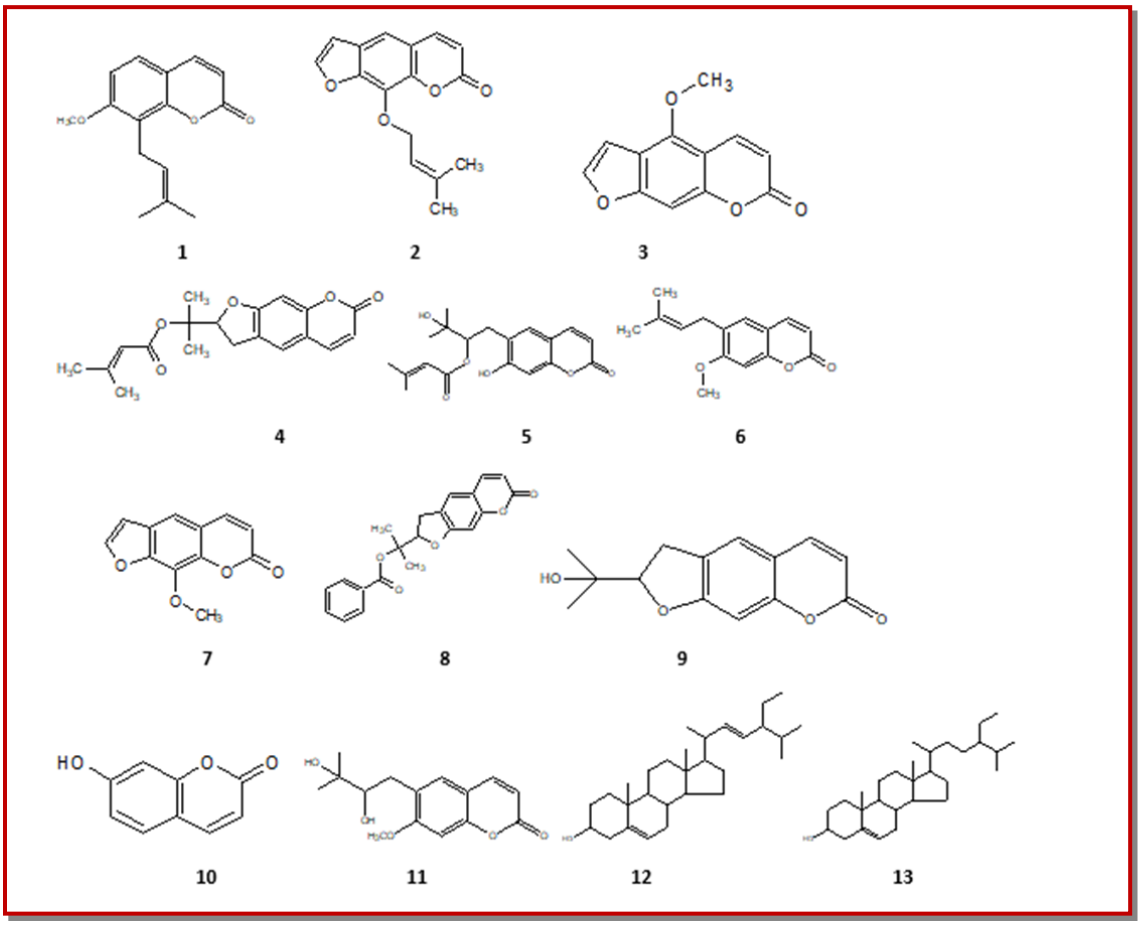

Figure 1: Chemical structures of compounds 1-13

Fr. G was fractioned by column chromatography over silica gel using *n*-hexane:ethyl acetate mixtures (70:30 and 90:10) consecutively and compound **8** was obtained (325 mg). Fr. H was submitted on a silica gel column using *n*-hexane:ethyl acetate (65:35) to yield compound **9** and the resulting fraction was chromatographed on the silica gel column using *n*-hexane:ethyl acetate (90:10) to give the compound **10**. Fr. I gave the compound **11** (320 mg). Compounds **1**-**4**, **5**, **7**, **8**, **10** and **12**-**13** were isolated by the same chromatographic methods in all species. Compounds **6** and **11** were isolated only from the dichloromethane fraction of the roots from *F. trachycarpa*. Compound **9** was isolated only from the dichloromethane fraction of the roots from *F. blancheana* (Figure 1).

a-Amylase inhibitory activity

a-Amylase inhibitory activity was established in accordance with the reported method (Nampoothiri et al., 2011) with slight modifications. 1% Starch solution (100 µL) in 20 mM sodium phosphate buffer (pH 6.9 with 6 mM sodium chloride) and sample solutions (100 µL) were incubated at 25°C for 10 min in 24-well microplate. Afterwards incubation, 100 µL *a*-amylase solution (0.5 mg/mL) was added to each well and the reaction mixtures were incubated at 25°C for 10 min. In order to stop the reaction after the incubation, dinitrosalicylic acid color reagent (200 µL) was added and then the microplate was incubated in a boiling water bath for 5 min and cooled at room temperature. It was taken 50 µL from each well and then was added to 96-well microplate. The reaction mixture was diluted by adding 200 µL distilled water and the absorbance was measured at 540 nm. Each assay for all samples was carried out in triplicate. Percentage inhibitions of all samples were calculated using the equation at following:

$$\%\text{Inhibition} = (1 - \frac{\triangle A_{sample}}{\triangle A_{control}}) \times 100$$

a-Glucosidase inhibitory activity

a-Glucosidase inhibitory activity was established by using a 96-well microtiter plate in accordance with the described method (Tao et al., 2013) with slight modifications. *p*-Nitro-phenyl-*a*-D-glucopyranoside (*p*-NPG) was used as the substrate and was prepared in 0.1 M potassium phosphate buffer (pH 6.8). *a*-Glucosidase (0.1 unit/mL, enzyme solution) was dissolved in the same buffer. The samples were dissolved in dimethyl sulfo-

xide (DMSO) and all samples (20 µL) together with the enzyme solution (20 µL) were mixed in the plate. Afterward, the substrate (40 µL) was added for initiation of the reaction and the mixture was incubated at 37°C for 40 min. After incubation, 0.2 M sodium carbonate (80 µL) in phosphate buffer (pH 6.8) was added to all wells in order to quench the reaction. The amount of released *p*-nitrophenol (pNP) was measured at 405 nm using a 96-well microplate reader. Each assay for all samples was carried out in triplicate. Percentage inhibitions of all samples were calculated using the equation at following:

$$\%\text{Inhibition} = (1 - \frac{\triangle A_{sample}}{\triangle A_{control}}) \times 100$$

Results and Discussion

Methanol extracts of the roots of three *Ferulago* species were fractionated using solvents with different polarities (dichloromethane, ethyl acetate and *n*-butanol) and the obtained fractions were evaluated for their *a*-amylase and *a*-glucosidase inhibitory activities. The active dichloromethane extracts were subjected to column chromatography over silica gel and sephadex LH-20. As the result, eleven coumarins osthole (**1**) (Sajjadi et al., 2009), imperatorin (**2**) (Muller et al., 2004), bergapten (**3**) (Stevenson et al., 2003), prantschimgin (**4**) (Sajjadi et al., 2015), grandivitinol (**5**) (Abyshe et al., 1977), suberosin (**6**) (Tabanca et al., 2016), xanthotoxin (**7**) (Stevenson et al., 2003), felamidin (**8**) (Kilic et al., 2006), marmesin (**9**) (Abreu et al., 2010), umbelliferone (**10**) (Singh et al., 2010), ulopterol (**11**) (Doganca et al., 1979) and a sterol mixture consisted of stigmasterol (**12**), β-sitosterol (**13**) (Woldeyes et al., 2012) (Figure 1) were isolated and identified.

The extracts and compounds **1**-**11**, obtained via bioassay guided fractionation and isolation process, were evaluated for their *in vitro a*-amylase and *a*-glucosidase inhibitory activities. The IC_{50} values and inhibitory effects (%) are given in Table II. Acarbose was used as a reference standard for both assays. Dichloromethane extracts of roots from *F. blancheana, F. pachyloba* and *F. trachycarpa* showed significant activities against *a*-glucosidase with IC_{50} value of 2.0, 2.0 and 0.3 mg/mL, respectively. Among the tested compounds felamidin (IC_{50} 0.4 mg/mL) possessed the best inhibitory activity which was more potent than acarbose (IC_{50} 5.0 mg/mL). Suberosin, osthole, imperatorin, prantschimgin and marmesin also showed *a*-glucosidase inhibitory activity (IC_{50} 0.9, 1.0, 1.2, 1.9, 3.0 mg/mL, respectively) which had lower effect than felamidin but stronger than acarbose. On the other hand, none of the extracts showed meaningful *a*-amylase inhibitory activity, while acarbose indicated 82.3% inhibition at a concentration of 1 mg/mL. These results indicate that felamidin was eleven times more effective than acarbose against *a*-glucosidase. To our knowledge, no previous study have been reported on *a*-glucosidase and *a*-amylase inhibitory activities of *F. blancheana, F. pachyloba* and *F. trachycarpa* and the isolated coumarins prantschimgin, felamidin, grandivitinol and suberosin. Also this is the first report on phytochemical analysis of these species. Our results are similar to the previous studies performed on related coumarins. Shalaby et al. (2014) found that imperatorin (at 1000 µg/mL α-glucosidase inhibition% was found to be 69.7 ± 3.7 and we found an inhibition of 89.9 ± 0.9% at a concentration of 5000 µg/mL) showed appreciable antidiabetic activity. Comparing these results with previous studies in which *a*-glucosidase IC_{50} value of umbelliferone was found to be 7.8 ± 0.1 µg/mL, we have found a higher inhibitory activity with 9.3 mg/mL (Ramith et al., 2014). Comparing these results with another previous study in which *a*-glucosidase IC_{50} value of umbelliferone was 0.5 mg/mL at 0.5 mg/mL, the inhibitory activity that we have found was again higher (Ayyasamy and Rajamanickam, 2015).

Conclusion

Among the compounds isolated from CH_2Cl_2 fractions of *F. blancheana, F. pachyloba* and *F. trachycarpa* roots, coumarins were determined the main chemical constituents of these fractions. The most potent compounds were felamidin and suberosin.

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Conflict of Interest

Authors declare no conflict of interest

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Table II

α-Glucosidase inhibitory activities of extracts, fractions and compounds from *Ferulago blancheana*, *F. pachyloba* and *F. trachycarpa*

Species	Extracts/fractions/ compounds	Concentration (μg/mL)	*a*-Glucosidase inhibition (%)	IC_{50} value (mg/mL)
F. blancheana	Methanol extract	5000	77.3 ± 0.1	2.2
	Methanol extract	2000	49.2 ± 0.5	2.2
	Dichloromethane fraction	5000	79.8 ± 1.0	2.0
	Dichloromethane fraction	2000	50.2 ± 0.6	2.0
	Ethyl acetate fraction	5000	ND	ND
	n-Butanol fraction	5000	ND	ND
	Aqueous residue fraction	5000	ND	ND
F. pachyloba	Methanol extract	5000	68.2 ± 0.7	3.2
	Methanol extract	2000	40.7 ± 0.1	3.2
	Dichloromethane fraction	5000	89.9 ± 0.5	2.0
	Dichloromethane fraction	2000	52.8 ± 0.1	2.0
	Ethyl acetate fraction	5000	72.1 ± 0.2	3.0
	Ethyl acetate fraction	2000	40.1 ± 0.1	3.0
	n-Butanol fraction	5000	ND	ND
	Aqueous residue fraction	5000	ND	ND
	Aqueous extract	5000	ND	ND
F. trachycarpa	Methanol extract	5000	88.7 ± 0.7	0.4
	Methanol extract	2000	82.1 ± 0.2	0.4
	Dichloromethane fraction	5000	89.1 ± 0.2	0.3
	Dichloromethane fraction	2000	85.3 ± 0.4	0.3
	Ethyl acetate fraction	5000	ND	ND
	n-Butanol fraction	5000	ND	ND
	Aqueous residue fraction	5000	ND	ND
	Aqueous extract	5000	ND	ND
Osthole		5000	93.3 ± 0.3	1.0
		2000	84.3 ± 1.7	1.0
Imperatorin		5000	89.0 ± 0.9	1.2
		2000	63.1 ± 0.7	1.2
Bergapten		5000	42.3 ± 0.4	6.1
		2000	39.7 ± 2.4	6.1
Prantschimgin		5000	68.2 ± 0.4	1.9
		2000	52.0 ± 0.0	1.9
Grandivitinol		5000	12.3 ± 0.4	20.0
		2000	7.8 ± 0.7	20.0
Suberosin		5000	88.9 ± 1.1	0.9
		2000	81.6 ± 1.2	0.9
Xanthotoxin		5000	45.8 ± 4.8	5.4
		2000	38.0 ± 8.6	5.4
Felamidin		5000	94.6 ± 0.1	0.4
		2000	64.9 ± 2.1	0.4
Marmesin		5000	84.8 ± 3.2	3.0
		2000	32.8 ± 2.2	3.0
Umbelliferone		5000	10.3 ± 0.5	9.3
		2000	8.8 ± 0.0	9.3
Ulopterol		5000	50.6 ± 2.8	5.1
		2000	42.9 ± 3.1	5.1
Acarbose		5000	50.8 ± 2.5	5.0
		2000	29.4 ± 1.7	5.0

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