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Ferulone A and ferulone B: two new coumarinesters from *Ferula orientalis* L. roots

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Abstract

Ferula orientalis (Apiaceae) is a well known perennial herb growing wild in Iran used in traditional medicine. To perform phytochemical studies, dried ground roots of *F. orientalis* were sequentially Soxhlet-extracted using *n*-hexane, dichloromethane and methanol. A combination of vacuum liquid chromatography and preparative thin layer chromatographic analyses were performed to isolate coumarin esters. The structures of the isolated compounds were elucidated by spectroscopic means, and *in vitro* free-radical-scavenging property was determined by the DPPH assay. Two new coumarin esters, 7-*O*-(4,8,12,16-tetrahydroxy-4,8,12,16-tetramethyl-heptadecanoyl)-coumarin and 7-*O*-(4-hydroxy-4,8,12-trimethyl-trideca-7,11-dienoyl)-coumarin, named ferulone A and ferulone B, respectively, were isolated from the *n*-hexane extract of the roots of *F. orientalis*. Both compounds showed a low level of free-radical-scavenging property with the RC₅₀ values of 0.252 and 0.556 mg/mL for compounds 1 and 2, respectively, as opposed to that of the positive control (quercetin) 0.004 mg/mL. This is the first report on the purification of coumarin esters from the genus *Ferula*.

Keywords: *Ferula orientalis*, ferulone, free-radical-scavenging, DPPH, umbelliferone,

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1. Introduction

Ferula orientalis L. (Apiaceae) of the subgenus *Peucedanoides* (Boiss.) Korovin is a well known medicinal plant (height: 100-150 cm), and one of the *ca.* 150 species of the genus *Ferula* L., which are widely distributed throughout the central and western Asia and the Mediterranean region (Miskiet al. 1987). It grows on rocky steps at 1600-2900 m, and has distinguishable yellow flowers, which bloom during late May and June (Davis 1971). Different species of *Ferula* were commonly named as Anghozeh, Koma, Sekbineh and Barijeh in Iran where they are used as adulterant, culinary spice and medicinal plants (Mozefferian 2003; Iranshahy & Iranshahi 2011). *Ferula* species are used in traditional medicine to treat flatulence and as an anticonvulsant, stimulant, expectorant and cancer chemopreventer (Iranshahi et al. 2008; Bagheriet al. 2010).

Previous studies on *F. orientalis* revealed its antioxidant (Kartalet al. 2007) and antifungal (Alinezhadet al. 2011) properties, and the presence of daucane and germacrane-type sesquiterpenes (Miskiet al. 1987). We previously described a ester coumarin from *F. persica* roots (Razavi & Janani 2015).

In continuation of our work on the genus *Ferula* (Auziet al. 2008; Geroushiet al. 2010), we now report on the isolation, identification and free-radical-scavenging property of two new coumarin esters, named ferulone A (**1**) and ferulone B (**2**) (Figure 1), from the roots of *F. orientalis*.

2. Results and discussion

Chromatographic analyses of the *n*-hexane extract of the roots of *F. orientalis* afforded two new coumarin esters, which were identified as 7-*O*-(4,8,12,16-tetrahydroxy-4,8,12,16-tetramethyl-heptadecanoyl)-coumarin (**1**, named ferulone A) and 7-*O*-(4-hydroxy-4,8,12-trimethyl-trideca-7,11-dienoyl)-coumarin (**2**, named ferulone B) by spectroscopic means (UV-Vis, IR, MS and 1D and 2D NMR).

Compound **1** was isolated as a yellowish-brown color oily substance, while compound **2** was a brown oil. The UV absorption maxima at 320, 270, 265, 259 and 252 nm suggested that compounds **1** and **2** were coumarins. In the ^1H NMR spectrum of **1** (Table S1), the doublets (integrating for 1H each) at $\delta_{\text{H}} 6.26$ and 7.64 with the coupling constant $J = 9.5$ Hz were the signature peaks for a coumarin nucleus without any oxygenation at C-5 (Murray et al. 1982). There were three aromatic signals, a doublet at $\delta_{\text{H}} 7.37$ ($J = 8.5$ Hz), a doublet of a doublet at $\delta_{\text{H}} 6.84$ ($J = 2.0, 8.5$ Hz) and a doublet at $\delta_{\text{H}} 6.82$ ($J = 2.0$ Hz), corresponding to *ortho*, *ortho-meta* and *meta* couplings among the aromatic protons suggesting a usual oxygenation at C-7 on the coumarin nucleus, i.e., a classic umbelliferone (**3**) skeleton (Figure 1) (Murray 1982; Kauret et al., 2012). In addition to the ^1H NMR signals assignable to a 7-oxygenated coumarin nucleus (**3**), there were signals for five methyl groups in the region of $\delta_{\text{H}} 1.17$ - 1.22 , and overlapped peaks in the region of $\delta_{\text{H}} 1.11$ - 2.29 , integrated for 22 protons and assignable to 11 aliphatic methylene groups, suggesting the presence of a long-chain fatty acid moiety in the molecule. In the ^{13}C NMR (Table S1, Figure S2) spectrum of **1**, in addition the usual signals attributable to an umbelliferone (**3**) skeleton, there were signals for an ester carbonyl group at $\delta_{\text{C}} 170.5$, five methyl groups at $\delta_{\text{C}} 18.0, 21.0, 22.7, 22.8$ and 21.7 , ten methylene signals in the region of $\delta_{\text{C}} 24.2$ - 31.4 , and a methylene signal at $\delta_{\text{C}} 43.6$, assignable to the methylene next to the ester carbonyl functionality, and four oxygenated quaternary carbons in the region of $\delta_{\text{C}} 67.7$ - 74.7 . All these signals further supported the presence of a long-chain fatty acid moiety. With the help of a combination of ^1H - ^1H COSY and ^1H - ^{13}C HMBC (Figure S1, Table S2) and ^1H - ^{13}C HSQC, these signals could be assigned unambiguously to a 4,8,12,16-tetrahydroxy-4,8,12,16-tetramethyl-heptadecanoyl moiety, which could only be ester-linked to C-7 of the umbelliferone (**3**) nucleus. The ESIMS spectrum of **1** revealed the *pseudo*-molecular ion $[\text{M}+\text{H}]^+$ at m/z 535, and in the HRMS, this ion was observed at m/z 535.3270 (calculated 535.3271 for $\text{C}_{30}\text{H}_{47}\text{O}_8$) confirming the molecular formula $\text{C}_{30}\text{H}_{46}\text{O}_8$ for coumarin **1**. Thus, taking all these spectroscopic data into account, coumarin **1** could be identified unequivocally as 7-*O*-(4,8,12,16-tetrahydroxy-

4,8,12,16-tetramethyl-heptadecanoyl)-coumarin, which, to the best of our knowledge, is a new natural product.

The ^1H NMR and ^{13}C NMR signals (Table S1) for compound **2** were quite similar to those of coumarin **1**, especially the signals associated with the coumarin nucleus, suggesting that this compound also had an umbelliferone (**3**) skeleton (Figure 1). However, the signals which were not associated with the umbelliferone moiety, were significantly different from those of compound **1**. In the ^1H NMR spectrum, in addition to signals assignable to an umbelliferone (**3**) nucleus, there were signals for four methyl groups in the region of δ_{H} 1.23-1.71, three of which [δ_{H} 1.45, 1.66 and 1.71] could be assigned to methyl groups directly linked to olefinic quaternary carbons, and overlapped peaks in the region of δ_{H} 1.20-2.29, integrated for 12 protons and assignable to six aliphatic methylene groups, and signals for two olefinic methine at δ_{H} 5.00-5.55, suggested the presence of an unsaturated long-chain fatty acid moiety in the molecule. In the ^{13}C NMR (Table S1, Figure S3) spectrum of **2**, there were signals for an ester carbonyl group at δ_{C} 170.5, four methyl groups at δ_{C} 22.9, 27.9, 28.9 and 29.7, and five methylene signals in the region of δ_{C} 26.2-32.4, and a methylene signal at δ_{C} 43.7 assignable to the methylene next to the ester carbonyl functionality, two olefinic methine signals at δ_{C} 119.2 and 124.5, and two olefinic quaternary carbons at δ_{C} 132.5 and 131.6. All these signals further supported the presence of a long-chain unsaturated fatty acid moiety in the molecule. With the help of a combination of ^1H - ^1H COSY and ^1H - ^{13}C HMBC (Figure S1, Table S2) and ^1H - ^{13}C HSQC, these signals could be assigned to a 4-hydroxy-4,8,12-trimethyl-trideca-7,11-dienoyl moiety, which could only be ester-linked to C-7 of the umbelliferone (**3**) nucleus as in compound **1**. The ESIMS spectrum of **2** revealed the *pseudo*-molecular ion $[\text{M}+\text{H}]^+$ at m/z 413, and in the HRMS, this ion was observed at m/z 413.2326 (calculated 413.2328 for $\text{C}_{25}\text{H}_{33}\text{O}_5$) confirming the molecular formula $\text{C}_{25}\text{H}_{32}\text{O}_5$ for coumarin **2**. Thus, coumarin **2** could be identified unambiguously as 7-*O*-(4-hydroxy-4,8,12-trimethyl-trideca-7,11-dienoyl)-coumarin, which, to the best of our knowledge, is a new natural product.

The *in vitro* free-radical-scavenging activities of the isolated compounds were evaluated by the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay (Takao et al., 1994; Kumarasamy et al. 2002; Chima et al. 2014). Compounds **1** and **2** exhibited low level of free-radical-scavenging property, with the RC_{50} values of 0.252 and 0.556 mg/mL as opposed to that of the positive control (quercetin) 0.004 mg/mL.

A review of literature showed that several coumarins with various sesquiterpenyl moieties have already been reported from different species of the genus *Ferula* (El-Razek et al. 2001; Iranshahiet al. 2010a,b; Bashir et al. 2014; Kasaian et al. 2014; Asghari et al. 2015). We previously described a ester coumarin from *F. persica* roots, another common *Ferula* species in Iran (Razavi & Janani 2015). The identified ester coumarin, ferulone c, has similar structure with two ester coumarins 2w3 isolated from *F. orientalis* in the present work. It has a ester moiety like ferulone B ones with just three hydroxyl group. It can be point out that beside of sesquiterpen coumarins, ester coumarins may be attribute of *Ferula* genus, as well as. It was previously well known that sesquiterpene coumarins from *Ferula* species indicated various bioactivity like cytotoxic and anti-inflammatory properties (Nazari & Iranshahi 2011; Zarei et al. 2012; Kasaian et al. 2013; Kasaian et al. 2015). Although ester coumarins have not considerable antioxidant potential, It can be assumed that ester coumarins might be exhibit different biological activities. Further investigations are need to confirm the hypothesis.

3. Experimental

3.1. General procedure

PG instrument T80+ spectrometer was used to determine UV spectra of compounds in MeOH. NMR Spectra were obtained in a Bruker AVANCE 400 MHz NMR spectrometer (¹H: 400 and ¹³C: 100 MHz) in CDCl₃, and the residual solvent peaks were used as internal standard; HMBC spectra were optimized for a long-range J(H,C) of 9 Hz. A Finnigan MAT95 spectrometer was used to obtain mass spectra of the compounds.

3.2. Plant material

The roots of *Ferula orientalis* L. were collected from Khalkhal in the province of Ardabil, in May 2011, and a voucher specimen (voucher no. 1390-2) representing this collection has been deposited with the Herbarium of the Department of Biology, Faculty of Sciences, Mohaghegh Ardabili University, Iran.

3.3. Extraction and isolation

Dried ground roots of *F. orientalis* (150 g) were extracted sequentially with *n*-hexane, dichloromethane and methanol (MeOH), 500 mL each, using a Soxhlet apparatus. The extracts were dried under vacuum. The *n*-hexane extract (3 g) was subjected to Vacuum Liquid Chromatography (VLC) on silica gel, eluting with solvent mixtures of increasing

polarity: 100% *n*-hexane-ethyl acetate (EtOAc), 100% EtOAc and 100% MeOH, to yield a number of fractions, which upon initial Thin Layer Chromatographic (TLC) analyses, were grouped into 13 main fractions. A mixture of fractions 7 and 8 (50% EtOAc in *n*-hexane, and 60% EtOAc in *n*-hexane) was further analysed by preparative-TLC (mobile phase = 5% acetone in chloroform) to yield compound **2** (13.3 mg, $R_f = 0.62$, blue fluorescent). The fraction of 100% MeOH was further analysed by preparative-TLC (mobile phase 10% acetone in chloroform) to yield compound **1** (12.1 mg, $R_f = 0.40$, blue fluorescent). The structures of the isolated compounds were elucidated by spectroscopic means.

Ferulone A [7-*O*-(4,8,12,16-tetrahydroxy-4,8,12,16-tetramethyl-heptadecanoyl)-coumarin, **1**, 12.1 mg]. Yellow-brown oil. UV λ_{max} (MeOH) nm: 320, 270, 265, 259 and 252. IR ν_{max} (CHCl₃) cm⁻¹: 3437, 2925, 2853, 1734, 1563, 1428, 1248, 1125, 968, 893, 836, 486; ¹H NMR (400 MHz, CD₃OD): 6.26(1H, d, $J = 9.5$ Hz, H-3), 7.64(1H, d, $J = 9.5$ Hz, H-4), 7.37(1H, d, $J = 8.5$ Hz, H-5), 6.84(1H, d, $J = 8.5, 2.0$ Hz, H-6), 6.82(1H, d, $J = 2$, H-8), 2.28(2H, dd, $J = 7.5, 4.5$ Hz, H-2'), 1.11-2.29 (overlapes peaks, H-3', H-5', H-6', H-7', H-9', H-10', H-11', H-13', H-14', H-15'), 1.22(3H, s, H-4'-Me), 1.19(3H, s, H-8'-Me), 1.19(3H, s, H-12'-Me), 1.17(3H, s, H-16'-Me), 1.20(3H, s, H-16'-Me); ¹³C NMR (100 MHz, CD₃OD): 161.8 (C-2), 112.9 (C-3), 143.3 (C-4), 128.7 (C-5), 113.3 (C-6), 160.1 (C-7), 101.6 (C-8), 156.0 (C-9), 112.6 (C-10), 170.5 (C-1'), 43.6 (C-2'), 31.4 (C-3'), 73.7 (C-4'), 22.8 (C-4'-Me), 31.4 (C-5'), 28.2 (C-6'), 30.8 (C-7'), 73.7 (C-8'), 22.7 (C-8'-Me), 30.7 (C-9'), 24.2 (C-10'), 30.7 (C-11'), 73.6 (C-12'), 21.7 (C-12'-Me), 30.2 (C-13'), 24.2 (C-14'), 30.2 (C-15'), 67.7 (C-16'), 21.0, 18.0 (C-16'-Me), see also Table S1; ¹H-¹H Cosy, HMBC and HSQC correlations: see Table S2; HR-ESI-MS: 535.3270 ([M+H]⁺, C₃₀H₄₇O₈; calc. 535.3271).

Ferulone B [7-*O*-(4-hydroxy-4,8,12-trimethyl-trideca-7,11-dienoyl)-coumarin, **2**, 13.3 mg]. Brown oil. UV λ_{max} (MeOH) nm: 316, 260, 264, 257, 251 and 246 nm. IR ν_{max} (CHCl₃) cm⁻¹: 3448, 2924, 2958, 2851, 1737, 1568, 1187, 830, 719, 639, 518; 476; ¹H NMR (400 MHz, CD₃OD): 6.28(1H, d, $J = 9.5$ Hz, H-3), 7.66(1H, d, $J = 9.5$ Hz, H-4), 7.56(1H, d, $J = 8.5$ Hz, H-5), 7.15(1H, d, $J = 8.5, 2.0$ Hz, H-6), 7.02(1H, s, H-8), 2.27(2H, dd, $J = 7.5, 4.5$ Hz, H-2'), 1.20-2.29 (overlapes peaks, H-3', H-5', H-6', H-9', H-10'), 5.02(2H, bt, H-7'), 5.53(2H, bt, H-11'), 1.23(3H, s, H-4'-Me), 1.66(3H, s, H-8'-Me), 1.458(3H, s, H-12'-Me), 1.71(3H, s, H-12'-Me); ¹³C NMR (100 MHz, CD₃OD): 162.0 (C-2), 113.1 (C-3), 143.5 (C-4), 128.4 (C-5), 113.4 (C-6), 161.2 (C-7), 101.7 (C-8), 155.9 (C-9), 112.6 (C-10), 170.5 (C-1'), 43.7 (C-2'), 31.4 (C-3'), 68.2 (C-

4'), 22.9(C-4'-Me), 31.3(C-5'), 32.0(C-6'), 119.2(C-7'), 132.5(C-8'), 27.9(C-8'-Me), 30.6(C-9'), 32.3(C-10'), 124.5(C-11'), 131.6(C-12'), 28.9, 29.7(C-12'-Me), see also Table S1; ¹H-¹H Cosy, HMBC and HSQC correlations: see Table S2; HR-ESI-MS: 413.2326 ([M+H]⁺, C₂₅H₃₃O₅; calc. 413.2328).

3.4. Free-radical-scavenging activity (the DPPH assay)

1,1-Diphenyl-2-picrylhydrazyl (DPPH), molecular formula C₁₈H₁₂N₅O₆, was obtained from FlukaChemie AG, CH-Buchs. The method of Takao *et al.* (1994) was adopted with suitable modifications (Kumarasamy *et al.*, 2002; Chima *et al.*, 2014). A solution of DPPH (80 µg/mL) in MeOH was used. The test samples were dissolved in MeOH to obtain a concentration of 1 mg/mL. Ten-fold dilutions were conducted with the stock solutions of test compounds to obtain concentrations of 0.1, 0.01, 0.001, 0.0001 and 0.00001 mg/mL. Diluted solutions (1 mL each) were mixed with DPPH (1 mL) and allowed 30 min for any reaction to occur. The absorbance was recorded at 517 nm. The experiment was performed in triplicate, and average absorption was noted for each concentration. Data were processed using the EXCEL, and the concentration that caused a 50% reduction in DPPH absorbance at 517 nm (RC₅₀) was calculated. The same procedure was applied for the positive control, quercetin.

4. Conclusion

To the best of our knowledge, ferulone A and B, are new natural products of ester coumarin class. It has previously been demonstrated that coumarins display several biological activities (Murray *et al.* 1982; Razavi & Zarrini 2010; Razavi *et al.* 2010; Razavi 2011). Therefore, it is reasonable to assume that reported pharmacological properties of *F. orientalis* might be, at least partly, owing to presence of coumarins in its roots.

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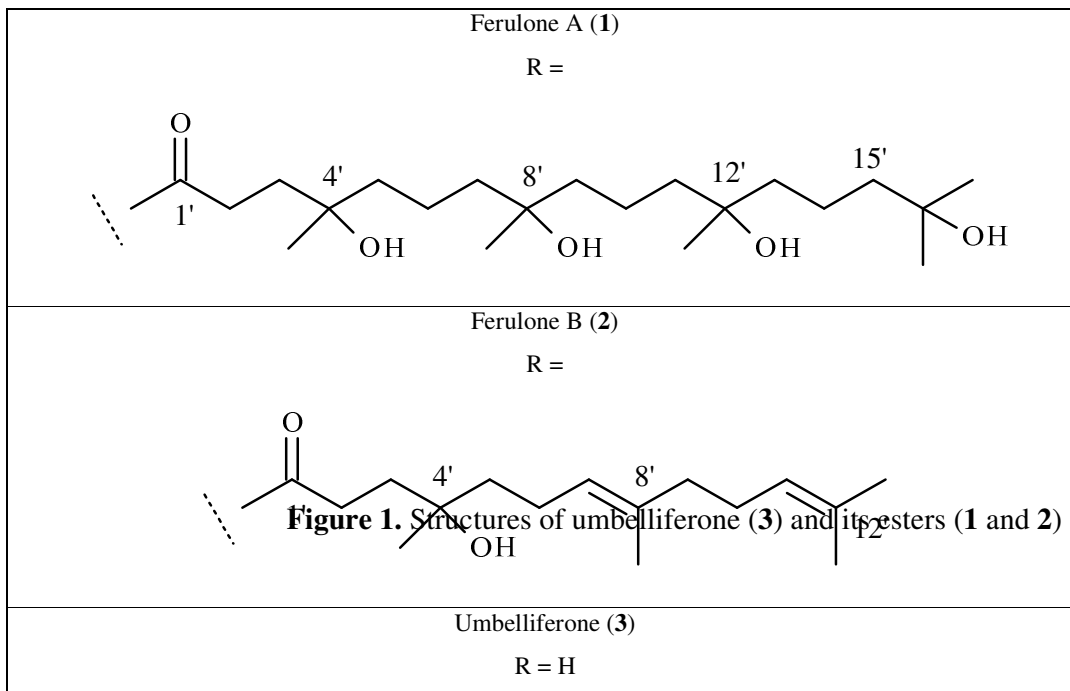
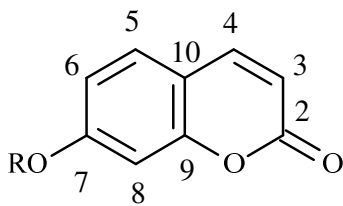


Figure 1. Structures of umbelliferone (3) and its esters (1 and 2)

Figure1. Structures of compound 1 and 2