Revista Brasileira de Farmacognosia 28 (2018) 421–424

Brazilian Journal of Pharmacognosy
REVISTA BRASILEIRA DE FARMACOGNOSIA
www.elsevier.com/locate/bjp

Original Article

A new feruloyl glyceride from the roots of Asian rice (*Oryza sativa*)

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ARTICLE INFO

Article history:
Received 3 February 2018
Accepted 18 May 2018
Available online 13 June 2018

Keywords:
Asian rice
Feruloyl glycerides
LC/MS-guided isolation
Cytotoxicity

ABSTRACT

Oryza sativa L., Poaceae, is the most important staple food in the world and provides food for more than half of the world's population. The roots of *O. sativa* have been used as a traditional medicine in Korea. As part of our continuing efforts to explore structurally new compounds from Korean natural resources, two feruloyl glycerides, 2-*O*-(*E*)-feruloyl glyceride (**1**) and 2-*O*-(*Z*)-feruloyl glyceride (**2**), which is a new compound, together with one known flavonoid, 8-hydroxyacacetin (**3**), were isolated from the ethanolic extract of the roots of *O. sativa* using an LC/MS-guided isolation method. The chemical structure of compound **2** was elucidated based on comprehensive 1D and 2D NMR spectroscopic experiments and HR-ESIMS. This study represents the first report of feruloyl glycerides (**1–2**) identified in *O. sativa*. In addition, the identification of compound **3** is reported from Asian rice (*O. sativa*) for the first time. The cytotoxic activities of the isolates **1–3** were evaluated by determining their inhibitory effects on A2780 human ovarian carcinoma cells.

Introduction

Oryza sativa L., Poaceae, is the most important staple food in the world and provides food for more than half of the world's population (Khush, 2005). Its roots, which are called "Na-do-guen" in Korea, have been used as a traditional medicine in Korea and China to improve digestion, promote the production of body fluid, reduce fever, stop cold sweats, and treat diabetes mellitus (Hikino et al., 1986). A variety of therapeutic activities including anti-tumor (Kim et al., 2007), anti-fungal (Koga et al., 1997; Peters, 2006), anti-viral (Peters, 2006), anti-microbial (Prisic et al., 2004), and anti-melanogenic effects (Cho et al., 2015) have been reported for the extracts of *O. sativa*. Additionally, recent studies have examined the pharmacological activities of the roots of *O. sativa* such as skin-whitening (Cho et al., 2015), hypoglycemic (Hikino et al., 1986), and laxative activities (Sangle et al., 2016). Previous phytochemical investigations of this plant have shown the presence of a variety of chemical constituents including glycans (Hikino et al., 1986), phytosterols (Park et al., 2017), polysaccharides (Park et al., 2017), diterpenoids (Koga et al., 1997; Kato et al., 2002; Peters, 2006), gibberellins (Prisic et al., 2004; Peters, 2006), and phenolic compounds (Cho et al., 2015).

Despite several trials investigating the chemical components of *O. sativa*, there have been few reports on the chemical constituents present in the roots. As part of our continuing efforts to explore structurally new compounds from Korean natural resources (Eom et al., 2016; Lee et al., 2016, 2017a,b; Yu et al., 2016a,b, 2017; Kang et al., 2016a,b; Eom et al., 2017; Beemelmanns et al., 2017), we focused on the roots of Asian rice (*O. sativa*), which has been relatively neglected in the phytochemical research field, and investigated the chemical constituents from the EtOH extract of the roots. In the present study, our LC/MS analysis of the EtOH extract of *O. sativa* roots revealed that the EtOH extract contains 2-*O*-feruloyl glyceride, which had not been reported from *O. sativa*. A liquid chromatography (LC)/mass spectrometry (MS) guided isolation technique was applied for the separation of the target constituents to effectively identify potential new compounds. As a result, two feruloyl glycerides (**1–2**) including a new compound, 2-*O*-(*Z*)-feruloyl glyceride (**2**), together with one known flavonoid (**3**) were isolated from the EtOH extract. In the present study, we report the LC/MS-guided isolation of compounds **1–3** and their structural elucidation, along with their cytotoxic effects on a human ovarian carcinoma line.

Materials and methods

General experimental procedures

IR spectra were recorded with a Bruker IFS-66/S FT-IR spectrometer (Bruker, Karlsruhe, Germany). UV spectra were acquired on an Agilent 8453 UV-visible spectrophotometer (Agilent Technologies, Santa Clara, CA, USA). ESI and HR-ESI mass spectra were

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https://doi.org/10.1016/j.bjp.2018.05.004

recorded using a Waters Micromass Q-Tof Ultima ESI-TOF mass spectrometer (Waters, New York, NY, USA). NMR spectra, including those from ^{1}H–^{1}H COSY, HSQC, and HMBC, were recorded with a Bruker AVANCE III 700 NMR spectrometer operating at 700 MHz (^{1}H) and 175 MHz (^{13}C) (Bruker, Karlsruhe, Germany), with chemical shifts given in ppm (δ) for ^{1}H and ^{13}C NMR analyses. Semi-preparative HPLC was performed using a Shimadzu Prominence HPLC System with SPD-20A/20AV Series Prominence HPLC UV-Vis detectors (Shimadzu, Tokyo, Japan). LC/MS analysis was performed on an Agilent 1200 Series HPLC system equipped with a diode array detector and 6130 Series ESI mass spectrometer using an analytical Kinetex C18 100 Å column (100 × 2.1 mm i.d., 5 μm; Phenomenex, Torrance, CA, USA). Silica gel 60 (70–230 mesh and 230–400 mesh; Merck, Darmstadt, Germany) and RP-C_{18} silica gel (Merck, 40–63 μm) were used for column chromatography. The packing material for molecular sieve column chromatography was Sephadex LH-20 (Pharmacia, Uppsala, Sweden). Merck precoated silica gel F_{254} plates and RP-18 F_{254s} plates were used for thin-layer chromatography (TLC). Spots were detected after TLC under UV light or by heating after spraying with anisaldehyde-sulfuric acid.

Plant material

The roots of *Oryza sativa* L., Poaceae, were purchased at Kyungdong Market in Seoul, Korea, in October 2013, and the identity of the material was verified by one of the authors (K.H.K.). A voucher specimen (SKK-BBR-2014) was deposited in the herbarium of the School of Pharmacy, Sungkyunkwan University, Suwon, Korea.

Extraction and isolation

Oryza sativa roots (500 g) were air-dried and extracted three times with 95% aqueous EtOH at 60 °C for 24 h and then filtered using Whatman filter paper No. 2 (pore size: 8 μm). After evaporation of the filtrate in a laboratory freeze-dryer, 53 g of the resultant dried extract was obtained. The dried EtOH extract powder was dissolved in sterile distilled water, and a small aliquot of the EtOH extract was sequentially injected into LC/MS eluted with a gradient solvent system of MeOH/H_2O (1:9–1:0, flow rate of 0.3 ml/min, UV 254 nm), which revealed the presence of feruloyl glyceride with a molecular ion peak at *m/z* 269 $[M+H]^+$ in positive ESI mode by comparison with our house-built UV library in LC/MS. The EtOH extract in distilled water was solvent-partitioned with hexanes, dichloromethane (DCM), ethyl acetate (EtOAc), *n*-butanol (BuOH), and water (residue). Five fractions with increasing polarity, the hexane-soluble fraction (1.32 g), DCM-soluble faction (3.20 g), EtOAc-soluble fraction (0.41 g), *n*-BuOH-soluble fraction (4.15 g), and water residue, were obtained. All five fractions were subjected to LC/MS and eluted with a gradient solvent system of MeOH/H_2O (1:9–1:0, flow rate of 0.3 ml/min, UV 254 nm) to identify the target constituent, feruloyl glyceride. Based on the LC/MS data, the DCM-soluble fraction containing the target constituent was then separated by silica gel column chromatography (200 g, 3 × 100 cm) into nine fractions (D1-D9) according to the solvent mixture ratio of chloroform/methanol [200:1 (D1), 100:1 (D2), 50:1 (D3), 20:1 (D4), 10:1 (D5), 5:1 (D6), 2:1 (D7), 1:1 (D8), and 0:1 (D9)]. All nine fractions were subjected to LC/MS prior to purification for the target isolation of feruloyl glyceride, which revealed that fraction D3 contained the target constituent. Fraction D3 (350 mg) was further separated into nine fractions (D31–D39) using a Sephadex LH-20 column with 100% MeOH. LC/MS analysis of the nine subfractions indicated the presence of feruloyl glyceride in subfraction D37 (37 mg), which was separated utilizing semi-preparative reversed-phase HPLC with an isocratic solvent system of aqueous 60% MeOH (Phenomenex Luna Phenyl-hexyl column, 250 mm × 10 mm i.d., 10 μm) with a flow rate of 2 ml/min and UV 254 nm to isolate the two feruloyl glycerides, compound (**1**) (1.6 mg, t_R = 32.5 min) and compound (**2**) (0.8 mg, t_R = 34.1 min), together with compound (**3**) (0.8 mg, t_R = 39.5 min).

Table 1
^{1}H (700 MHz) and ^{13}C NMR (175 MHz) spectral data of **1–2** in CD_3OD (δ in ppm).

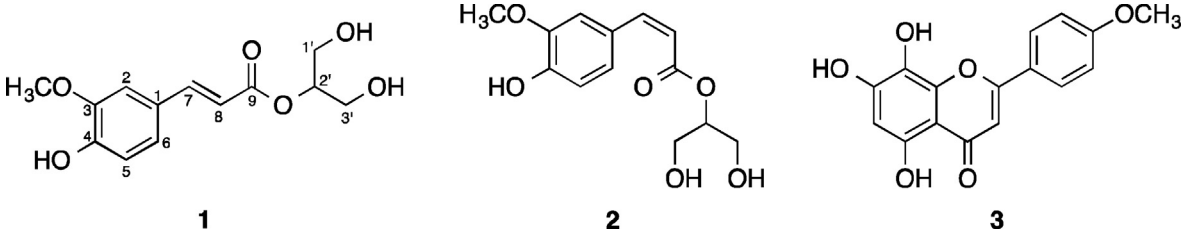
Position	1		2	
	δ_H	δ_C	δ_H	δ_C
1		127.1		126.8
2	7.16 d (2.0)	110.3	7.83 d (2.0)	114.5
3		148.5		142.2
4		147.3		148.9
5	6.78 d (8.0)	115.7	6.76 d (8.0)	115.2
6	7.06 dd (8.0, 2.0)	123.2	7.08 dd (8.0, 2.0)	124.8
7	7.68 d (16.0)	145.6	6.89 d (12.5)	146.1
8	6.36 d (16.0)	115.0	5.82 d (12.5)	118.6
9		167.8		168.0
1′	3.90 m; 3.86 m	62.3	3.90 m; 3.86 m	62.4
2′	4.29 dd (5.5, 1.5)	75.2	4.29 dd (5.5, 1.5)	75.0
3′	3.90 m; 3.86 m	62.3	3.90 m; 3.86 m	62.4
OCH_3	3.86 s	56.0	3.85 s	56.0

Assignments were based on 2D NMR including COSY, HSQC, and HMBC. Well-resolved couplings are expressed with coupling patterns and coupling constants in Hz in parentheses.

2-*O*-(*Z*)-Feruloyl glyceride (**2**): Colorless gum; UV (MeOH) λ_{max} (log ε) 248 (2.8) 300 (2.7) 328 (3.2) nm; IR (KBr) ν_{max}: 3350, 2942, 2834, 1718, 1452, 1029, 670 cm^{-1}. ^{1}H (700 MHz) and ^{13}C (175 MHz) NMR data, see Table 1; HR-ESIMS (positive-ion mode) *m/z*: 269.1028 $[M+H]^+$ (Calcd for $C_{13}H_{17}O_6$, 269.1025).

Cytotoxicity assay

The A2780 human ovarian carcinoma cell line was purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA) and maintained in Roswell Park Memorial Institute 1640 medium (RPMI 1640) (Cellgro, Manassas, VA, USA) supplemented with 10% fetal bovine serum (Gibco BRL, Carlsbad, CA, USA), 100 units/ml penicillin, and 100 mg/ml streptomycin with incubation at 37 °C in a humidified atmosphere with 5% CO_2. The A2780 cells were seeded at 1 × 10^4 cells/100 ml in 96-well plates. After incubation for 24 h, the cells were incubated in cell culture medium with or without test samples for an additional 24 h. Cell viability was determined using the MTT cell proliferation assay.



1 **2** **3**

Results and discussion

The dried roots of *O. sativa* were extracted with 95% EtOH and then filtered. After evaporation of the filtrate in a laboratory freeze-dryer, we obtained the resultant dried EtOH extract powder. LC/MS analysis of the extract deduced the presence of feruloyl glyceride with a molecular ion peak at *m/z* 269 $[M+H]^+$ in positive electrospray ionization (ESI) mode, by comparison with our house-built UV library in LC/MS. The major fragment at *m/z* 177 in $ESIMS^2$ indicated $[C_{10}H_9O_3]^+$, and another stable fragment at *m/z* 75 indicated $[C_3H_7O_2]^+$. Based on the molecular weight, fragmentation pattern, and UV absorption, the compound was tentatively identified as feruloyl glyceride. Since feruloyl glyceride has not been previously reported from *O. sativa*, LC/MS-guided isolation was carried out for the target separation of feruloyl glyceride. The high sensitivity and selectivity of the LC/MS-guided isolation method selectively reduced the analysis time and consequently enabled fast isolation of target compounds (Wang et al., 2016; Nørskov and Knudsen, 2016; Dong et al., 2017). The target compound, feruloyl glyceride, was isolated by open-column chromatography and semi-preparative HPLC monitored by LC/MS analysis, which led to identification of the fractions containing the desired compound. In other words, the final LC/MS analysis of subfraction D37 depicted peaks of feruloyl glycerides with a molecular ion peak at *m/z* 269 $[M+H]^+$ and UV absorptions of ferulic acid, which were isolated by semi-preparative HPLC. In addition, one flavonoid was isolated from the subfraction D37 during the isolation of the target compounds.

Compound **1** was isolated as a colorless gum and possessed the molecular formula of $C_{13}H_{16}O_6$ as deduced from the ESI-MS data of LC/MS analysis. The comparison with our house-built UV library in LC/MS revealed that compound **1** is a ferulic acid derivative. The ^1H NMR spectrum (Table 1) of **1** displayed a typical pattern of a feruloyl moiety, with two olefinic protons at δ_H 7.68 (1H, d, J = 16.0 Hz) and 6.36 (1H, d, J = 16.0 Hz); three aromatic ring protons at δ_H 7.16 (1H, d, J = 2.0 Hz), 7.06 (1H, dd, J = 8.0, 2.0 Hz), and 6.78 (1H, d, J = 8.0 Hz); and one methoxy group at δ_H 3.86 (3H, s). The ^{13}C NMR spectrum (Table 1) of **1** exhibited two olefinic carbons at δ_C 145.6 (C-7) and 115.0 (C-8), six aromatic ring carbons at δ_C 148.5 (C-3), 147.3 (C-4), 127.1 (C-1), 123.2 (C-6), 115.7 (C-5), and 110.3 (C-2), and one methoxy group carbon at δ_C 56.0 as well as a carboxyl carbon at δ_C 167.8 (C-9). In addition, the NMR data of **1** showed an additional glyceride unit with two oxygenated methylenes at δ_H 3.90 (2H, m) and 3.86 (2H, m)/δ_C 62.3 (C-1′ and C-3′) and one oxygenated methine at δ_H 4.29 (1H, dd, J = 5.5, 1.5 Hz). The coupling constant of the olefinic proton between C-7 and C-8 was 16.0 Hz, indicating that the double bond of **1** has a *trans*-configuration. Based on these data, the structure of **1** was elucidated as 2-*O*-(*E*)-feruloyl glyceride by detailed comparison of its spectroscopic data with previously reported values (Rocha et al., 2010).

Compound **2** shared the same planar structure and the same molecular formula $C_{13}H_{16}O_6$ as compound **1**, which was established based on ^1H and ^{13}C NMR data and positive-ion mode high resolution (HR)-ESI-MS ions detected at *m/z* 269.1028 $[M+H]^+$ (Calcd for $C_{13}H_{17}O_6$, 269.1025). The ^1H and ^{13}C NMR peaks and ^1H–^1H correlation spectroscopy (COSY), heteronuclear single quantum coherence spectroscopy (HSQC), and heteronuclear multiple bond correlation (HMBC) correlations of compound **2** were very similar to those of **1**, except for the aromatic region (Table 1). The ^1H NMR spectrum of **2** showed a *cis*-ferulic acid moiety with three aromatic ring protons at δ_H 7.83 (1H, d, J = 2.0 Hz), 7.08 (1H, dd, J = 8.0, 2.0 Hz), and 6.76 (1H, d, J = 8.0 Hz) and one methoxyl group at δ_H 3.85 (3H, s), as well as two double-bond protons at δ_H 6.89 (1H, d, J = 12.5 Hz) and 5.82 (1H, d, J = 12.5 Hz) with a lower coupling constant, corresponding to a *cis*-configuration (Bergman et al., 2001; Eom et al., 2017). Finally, the gross structure of **2** was

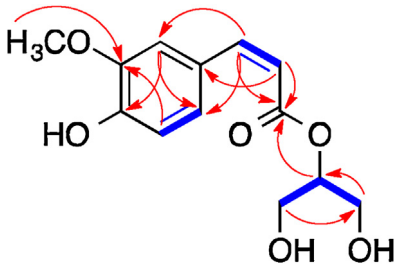


Fig. 1. Key ^1H–^1H COSY ( ) and HMBC ( ) correlations of **2**.

confirmed by the cross peaks in the ^1H–^1H COSY and HMBC spectra (Fig. 1), which revealed that the *cis*-ferulic acid moiety is linked to C-2 of the glyceride unit. Thus, compound **2** was determined to be 2-*O*-(*Z*)-feruloyl glyceride, which has not previously been reported. Interestingly, compounds **1** and **2** seem to be interconvertible to each other. The isomerization of the olefin unit from the *E* to *Z* form was expected owing to exposure to sunlight, and similar phenomena were observed in previous studies (Lewis et al., 1991; Sobolev et al., 2008; Kim et al., 2010).

Using a combination of ^1H and ^{13}C NMR and ESIMS data and comparing the spectroscopic data with previously reported values (Meselhy, 2003), the chemical structure of the isolated flavonoid (**3**) was determined as 8-hydroxyacacetin (**3**). This study represents the first report of feruloyl glycerides (**1–2**) identified in *O. sativa*. In addition, the identification of compound **3** is reported from Asian rice (*O. sativa*) for the first time.

The cytotoxic activities of the isolated compounds **1–3** were evaluated by determining their inhibitory effects on A2780 human ovarian carcinoma cells using the MTT assay (Peng et al., 2016; Taher et al., 2016; Jung et al., 2017; Aayadi et al., 2017). This assay revealed that the tested compounds **1–3** had minimal cytotoxicity against A2780 cells (IC_{50} > 100 μM).

Conclusions

Oryza sativa is the most important staple food in the world and its roots has long been used as a traditional medicine for many therapeutic purposes. The LC/MS-guided isolation of the EtOH extract of the roots of *O. sativa* led to the isolation of two feruloyl glycerides (**1–2**), 2-*O*-(*E*)-feruloyl glyceride (**1**) and 2-*O*-(*Z*)-feruloyl glyceride (**2**), which is a new compound, together with one known flavonoid, 8-hydroxyacacetin (**3**). This study represents the first report of feruloyl glycerides (**1–2**) identified in *O. sativa* and the identification of flavonoid **3** is reported from Asian rice (*O. sativa*) for the first time. The isolated compounds **1–3** had minimal cytotoxicity against A2780 human ovarian carcinoma cells (IC_{50} > 100 μM).

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Authors' contribution

TKL and HRK contributed the experiments. TKL and KHK prepared and wrote the manuscript. KTK and HRK contributed analysis

and discussion. KHK contributed the design of the project and reviewed the manuscript. All the authors have read the final manuscript and approved the submission.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT, & Future Planning (2015R1C1A1A02037383) and by the Ministry of Education (NRF-2012R1A5A2A28671860).

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