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Flavonol glycosides from *Reseda lutea* L

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ABSTRACT

Two new flavonol glycosides; kaempferol-3-*O*-[2-*O*-(β-D-xylopyranosyl)-3-*O*-(β-D-glucopyranosyl)]-α-L-rhamnopyranosyl-7-*O*- α-L-rhamnopyranoside (1) and kaempferol-3-*O*-[2-*O*-((6-*O*-*trans*-*p*-coumaryl)-β-D-glucopyranosyl)-3-*O*-(β-D-xylopyranosyl)]-α-L-rhamnopyranosyl-7-*O*- α-L-rhamnopyranoside (2) were isolated from the aerial parts of *Reseda lutea* L., together with five known flavonol glycosides. Structural elucidation of the compounds was based on both spectroscopic evidence and reference data comparison. The new compounds are the first tetrasaccharidic secondary metabolites isolated from Resedaceae family.

1. Introduction

Reseda L. is the largest genus of the Resedaceae family, with approximately 65 species mainly distributed in temperate areas of the western Palearctic, with a center of diversity in the Mediterranean basin and Southwestern Asia (Martín-Bravo et al., 2007). *Reseda* L. is represented by 18 taxa in Turkey, 10 of which are endemic to Turkey (Coode, 1965; Abdallah and de Wit, 1978; Martín-Bravo and Jiménez-Mejías, 2013; Çilden et al., 2018). Previous phytochemical investigations on this genus revealed the presence of flavonoids (Berrehal et al., 2006, 2012; El-Sayed et al., 2001), non-protein aminoacids (Meier et al., 1979), glucosinolates (Olsen and Soerenson, 1980) and alkaloids (Lutfullin et al., 1977; Nakhotov and Tadzhibaev, 1977).

The extracts and secondary metabolites of *Reseda* were reported to have antimicrobial, antioxidant (Kumarasamy et al., 2002; Berrehal et al., 2010; Benmerache et al., 2012), anti-inflammatory (Susplugas-Taillade et al., 1988; Bremner et al., 2009,), anti-HIV (Bedoya et al., 2001), antiproliferative and proapoptotic (Woelfle et al., 2010; Radulović et al., 2014), and neuroprotective (Kim et al., 2015) activities.

We here report the isolation and identification of two new compounds, a kaempferol tetraoside (**1**) and its *p*-coumaryl ester (**2**) together with five previously reported flavonoids.

2. Results and discussion

Structures of compounds **1** and **2** are shown in Fig. 1.

Compound **1** was isolated as a yellow amorphous powder and the molecular formula of **1** was determined as $C_{38}H_{48}O_{23}$ due to the sodium adduct ion peak at *m/z* 895.25803 $[M + Na]^+$ obtained by HRMS. In the IR spectrum, absorption bands for hydroxyl (3405 cm^{-1}), conjugated carbonyl (1657 cm^{-1}), and aromatic (1603 cm^{-1}, 1494 cm^{-1}, 1451 cm^{-1}) groups were apparent. The ^{1}H-NMR resonances of two *m*-coupled protons at δ 6.81 (d, J = 1.8 Hz) and 6.96 (d, J = 1.9 Hz), which correlated with carbons at δ 100.9 and 95.4 in the HSQC spectrum, were characteristic of the two *meta*-related 6- and 8- protons of a 5,7-dihydroxy A-ring of a flavonoid skeleton (Khallouki et al., 2000). Additionally, in the low-field of the ^{1}H-NMR spectrum, 4H were observed as coupled doublets (A_2B_2 system) at δ 8.09 (2H, d, J = 8.6 Hz, H-2' and H-6') and 7.44 (2H, d, J = 8.7 Hz, H-3' and H-5'), suggesting that the B-ring was para-disubstituted. Therefore, the aglycon moiety of **1** was characterized as flavonol or a flavonol substituted in C-3, a well-known flavonoid aglycone. The resonances of four anomeric protons, observed at δ 6.29 (s), 6.27 (s), 5.48 (d, J = 7.6 Hz) and 5.31 (d, J = 7.4 Hz), suggested that compound **1** was a tetra saccharidic kaempferol derivative. The structure of the oligosaccharide unit was elucidated using the 2D NMR experiments. The correlations deduced from the COSY spectrum allowed the assignments of all proton resonances within each sugar residue, starting from the well-isolated anomeric proton signals. HSQC experiment, which correlated all proton resonances with those of each corresponding carbon, permitted the assignments of the interglycosidic linkages by comparison of the observed carbon chemical shifts with those of the corresponding methylpyranosides, considering the known effects of glycosidation. Thus, on the basis of the proton and carbon chemical shifts, multiplicity of the signals and absolute values of coupling constants, the four sugar residues were identified as β-xylopyranosyl, β-glucopyranosyl and α-rhamnopyranosyl. The absolute configurations of the sugar residues

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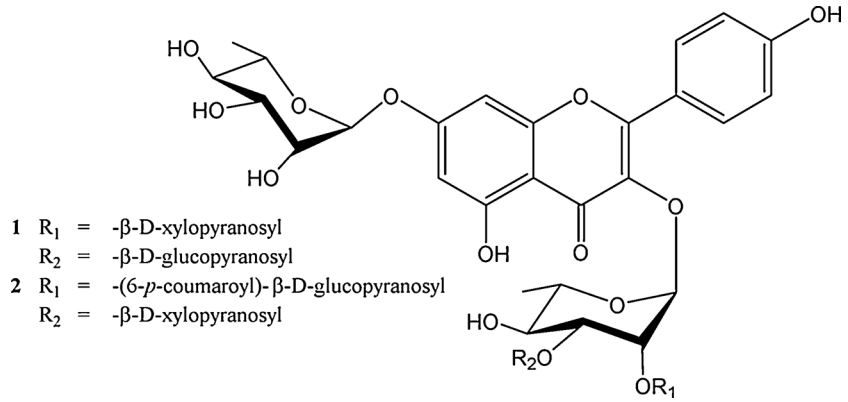

Fig. 1. Structures of compounds **1** and **2**.

were established to be D for glucose and xylose, and L for rhamnose based on the optical rotation data of the isolated sugars and taking into consideration the biogenetic evidence derived from *Reseda* flavonoids.

The absence of any ^{13}C-NMR glycosidation shifts for the 7-*O*-rhamnopyranosyl, xylopyranosyl and glucopyranosyl residues suggested these sugars to be terminal. The position of each sugar residue was unambiguously determined by the HMBC experiment (Fig. 2), which showed long-range correlations between H-1”$_{rhm}$ (δ 6.29 brs) and C-3 (δ 136.1), H-1”’$_{xyl}$ (δ 5.31) and C-2”$_{rhm}$ (δ 80.3), H-1””$_{glu}$ (δ 5.31) and C-3”$_{rhm}$ (δ 81.8), and H-1”””$_{rhm}$ (δ 6.27) and C-7 (δ 163.3). On the basis of these data, the structure of compound **1** was established as kaempferol-3-*O*-[2-*O*-(β-D-xylopyranosyl)-3-*O*-(β-D-glucopyranosyl)]-α-L-rhamnopyranosyl-7-*O*-α-L-rhamnopyranoside.

Compound **2** was also isolated as a yellow amorphous powder. The molecular formula of **2** was determined as $C_{47}H_{54}O_{25}$ from its HRMS (*m/z* 1041.29511 [M + Na]$^+$). The IR spectrum of **2** showed absorptions of ester carbonyl (1688 cm^{-1}), hydroxyl (3422 cm^{-1}), conjugated carbonyl (1655 cm^{-1}), aromatic (1604 cm^{-1}, 1494 cm^{-1}, 1451 cm^{-1}) groups. The ^{1}H- and ^{13}C NMR spectra of **2** showed the presence of aromatic and sugar moiety resonances.

The ^{1}H-NMR and COSY spectra revealed three distinct aromatic systems. First one displayed resonances at δ 7.48 (2H, d, *J* = 8.1 Hz, H-2”””” and H-6”””) and 6.97 (2H, d, *J* = 7.8 Hz, H-3”””” and H-5”””). Considering the coupling pattern, i.e., two *ortho* couplings, it was inferred that **2** had a *para* disubstituted-aromatic ring. A *trans* disubstituted double bond (δ 7.97, d, *J* = 15.9 Hz and δ 6.68, d, *J* = 15.9 Hz) was also observed. In the ^{13}C-NMR spectrum of **2**, the resonances for two olefinic carbons (δ 146.1 and δ 115.4), attributed to the *trans* double-bond system, and the carbonyl carbon resonance at δ 168.1 helped us to deduce a *p*-coumaryl residue in **2**. The long-range correlations in the HMBC spectrum between olefinic protons (H-7”””” and H-8”””) and carbonyl carbon (C-9”””)/aromatic carbons (C-2”””” and C-5”””) substantiated the presence of *p*-coumaric acid moiety. After subtraction of the 9 carbon resonances from the aromatic region, the remaining resonances were attributable to a flavonoid skeleton. Detailed inspection of the 1D NMR spectra revealed that the remaining aromatic systems were consistent with the presence of kaempferol as in **1** (Table 1 and Fig. 1). All the assignments of the aglycone moiety were secured by 2D NMR experiments, which also revealed that the oligosaccharide moieties of **2** were identical of compound **1**; however, a number of discrepancies were evident for glycosidic linkages. The HMBC spectrum (Fig. 3) displayed long-range correlations from H-1”$_{rhm}$ (δ 6.37) to C-3 (δ 136.1), H-1”’$_{glu}$ (δ 5.38) to C-2”$_{rhm}$ (δ 79.9), H-1””$_{xyl}$ (δ 5.47) to C-3”$_{rhm}$ (δ 82.0), and H-1”””$_{rhm}$ (δ 6.27) to C-7 (δ 163.3) verifying that the position of xylopyranosyl and glucopyranosyl residues switched in the structure of **2** compared to **1**. The ^{1}H-NMR spectrum of **2** also showed that methylene protons of glucose (H_2-6”’) shifted downfield to δ 5.15 (m) and 4.90 (dd, *J* = 11.6 and 7.4 Hz) confirming acylation at the C-6(*O*) position (Kim et al., 1998; Liu et al., 1999). The linkage of the *p*-coumaryl group to the C-6(*O*) of the glucose was also confirmed by the cross peak between the carbonyl carbon at δ 168.1 and H_2-6”’ at δ 4.90 (Bloor, 1999).

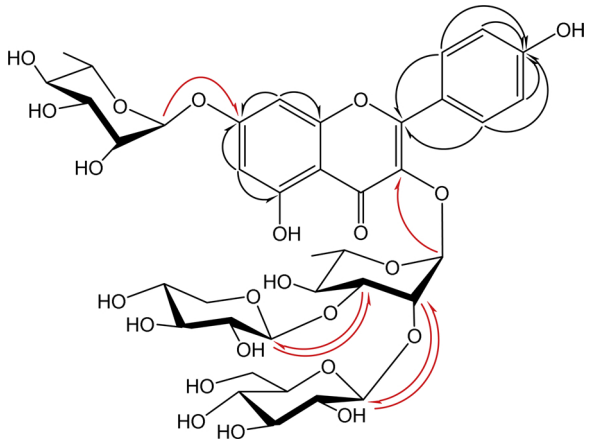

Fig. 2. Key HMBC's of compound **1** (arrows from H to C).

The absolute configuration of sugar units were established after hydrolysis of the flavonoid fraction of *R. lutea*, and confirmed by the optical rotation data of the isolated sugars and biogenetic considerations.

Consequently, the structure of **2** was established as kaempferol-3-*O*-[2-*O*-((6-*O*- *trans*-*p*-coumaryl)-β-D-glucopyranosyl)-3-*O*-(β-D-xylopyranosyl)]-α-L-rhamnopyranosyl-7-*O*-α-L-rhamnopyranoside.

The known compounds kaempferol-3-*O*-[2-*O*-(β-D-xylopyranosyl)]-α-L-rhamnopyranosyl-7-*O*-α-L-rhamnopyranoside (**3**), kaempferol-3-*O*-β-D-glucopyranosyl-7-*O*-α-L-rhamnopyranoside (**4a**), isorhamnetin-3-*O*-β-D-glucopyranosyl-7-*O*-α-L-rhamnopyranoside (**4b**), kaempferol-3,7-di-*O*-α–L-rhamnopyranoside (**5a**) and isorhamnetin-3,7-di-O-α-rhamnopyranoside (**5b**) were also isolated and identified by comparison of their ^{1}H-NMR spectra with literature data (Berrehal et al., 2012).

Secondary metabolites of Resedaceae family are mainly flavonoids with flavone, flavonol and isoflavone skeletons. The previous phytochemical investigations on *Reseda* genus revealed the presence of luteolin, luteolin-7-*O* glucoside, luteolin 4′-*O*-glucoside and apigenin *from R. luteola* (Woelfle et al., 2010; Moiteiro et al., 2008), whereas quercetin, isorhamnetin and kaempferol and their glycosides from *R. villosa* (Berrahal et al., 2006), *R. muricata* (El-Sayed et al., 2001) and *R. lutea* (Rzadkowska-Bodalska, 1969) were also identified. Moreover, Yuldashev et al. (1996) reported flavonol diglycosides of kaempferol, quercetin and isorhamnetin from *R. luteola*.

Two new compounds named kaempferol-3-*O*-[2-*O*-(β-D-xylopyranosyl)-3-*O*-(β-D-glucopyranosyl)]-α-L-rhamnopyranosyl-7-*O*- α-L-rhamnopyranoside and kaempferol-3-*O*-[2-*O*-((6-*O*-*trans*-*p*-coumaryl)-

Table 1
^{1}H-NMR and ^{13}C assignments of **1** and **2** in Pyridine-d5.

H/C	**1**		**2**	
	δ_H (*J* in Hz)	δ_C	δ_H (*J* in Hz)	δ_C
1				
2		158.9		158.5
3		136.1		136.1
4		179.6		179.5
5		162.9		162.8
6	6.81 d (1.8)	100.9	6.73 brs	100.9
7		163.3		163.3
8	6.96 d (1.9)	95.4	6.94 brs	95.3
9		157.5		157.5
10		107.5		107.5
1'		121.7		121.8
2'	8.09 d (8.6)	132.1	8.14 d (8.0)	132.1
3'	7.44 d (8.7)	117.2	7.41 d (7.9)	117.1
4'		162.7		162.6
5'	7.44 d (8.7)	117.2	7.41 d (7.9)	117.1
6'	8.09 d (8.6)	132.1	8.14 d (8.0)	132.1
α-L-Rhm (at C-3)			**α-L-Rhm (at C-3)**	
1"	6.29 brs	103	6.37 brs	102.6
2"	5.24 brs	80.3	5.26 brs	79.9
3"	4.83 dd (9.5, 3.1)	81.8	4.84 m	82.0
4"	4.36 m	72.3	4.36 m	72.1
5"	4.47 m	72.1	4.32 m	72.1
6"	1.37 d (6.0)	18.6	1.34 d (4.4)	18.8
β-D-Xyl (at C-2 of Rhm at C-3)			**β-D-Glu (at C-2 of Rhm at C-3)**	
1'"	5.31 d (7.4)	107.3	5.38 d (7.5)	107.0
2'"	4.0 m	76.0	3.97 m	76.0
3'"	4.24 m	78.8	4.25 m	78.7
4'"	4.15 m	71.5	4.02 m	72.3
5'"	4.30 m; 3.73 t (10.5)	67.8	4.17 m	76.3
6'"	–	–	4.90 dd (11.6, 7.4); 5.15 m	65.3
β-D-Glu (at C-3 of Rhm at C-3)			**β-D-Xyl (at C-3 of Rhm at C-3)**	
1""	5.48 d (7.6)	106.4	5.47 d (7.1)	106.8
2""	4.15 m	76.2	4.21 m	76.1
3""	4.23 m	78.6	4.14 m	78.7
4""	4.29 m	72.0	4.14 m	71.6
5""	4.00 m	79.1	4.31 dd (10.7, 4.0); 3.77 t (10.4)	67.9
6""	4.53 dd (11.6, 2.0); 4.36 m	63.1	–	–
α-L-Rhm (at C-7)			**α-L-Rhm (at C-7)**	
1"""	6.27 brs	100.5	6.27 brs	100.5
2"""	4.72 brs	72.1	4.70 brs	72.3
3"""	4.67 dd (9.1, 3.3)	72.9	4.60 m	72.8
4"""	4.39 m	74.0	4.40 m	74.1
5"""	4.30 m	71.9	4.36 m	71.9
6"""	1.66 d (6.0)	19.1	1.67 d (5.9)	19.4
			***p*-coumaric acid**	
1""""				126.4
2""""			7.48 d (8.1)	130.9
3""""			6.97 d (7.8)	117.0
4""""				161.8
5""""			6.97 d (7.8)	117.0
6""""			7.48 d (8.1)	130.9
7""""			7.97 d (15.9)	146.1
8""""			6.68 d (15.9)	115.4
9""""				168.1

β-D-glucopyranosyl)-3-*O*-(β-D-xylopyranosyl)]-α-L-rhamnopyranosyl 7-*O*- α-L-rhamnopyranoside are reported here as new ones as well as first tetrasaccharidic secondary metabolites from the family Resedaceae (El-Sayed et al., 2001; Berrahal et al., 2006; Berrehal et al., 2012).

3. Experimental

3.1. General procedures

High resolution mass spectra were obtained on Agilent 1200/6530 Instrument –HRTOFMS. IR spectra were obtained on Perkin Elmer Spectrum 100 FT-IR spectrometer. Optical rotation measurements were measured with ADP 410 Digital Polarimeter (Bellingham + Stanley Ltd.) in distilled H_2O. 1D and 2D (COSY, HMBC, HSQC and NOESY) NMR spectra were recorded on Varian 400-NMR (400 MHz) spectrometer with TMS as internal standard at room temperature. 2D NMR spectra were run using standard Varian pulse programs. Column chromatography was carried out on silica gel (JT Baker, 40 mm), Sephadex LH-20 (Amersham Biosciences, 17-0090-02). TLC analyses were carried out on silica gel 60 F_{254} (Merck) and RP-18 F_{254s} (Merck) pre-coated aluminum plates. Compounds were detected by UV (254–366 nm) and spraying 20% H_2SO_4 reagent followed by heating.

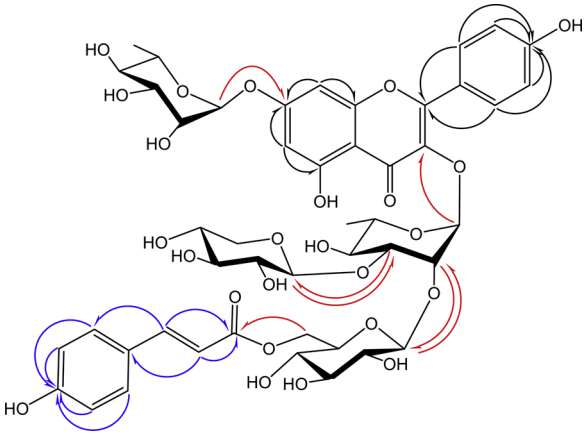

Fig. 3. Key HMBC's of compound **2** (arrows from H to C).

3.2. Plant material

R. lutea L. var. *lutea* L. was collected from Kagizman, Kars, Turkey in June 2017 (40°08′54.7″N; 43°06′44.1″E). The plant was confirmed by Dr. Ademi Fahri Pirhan (Deparment of Biology, Faculty of Sciences, Ege University, Izmir, Turkey). Voucher specimens (EGE 43,161) have been deposited at the herbarium of the Department of Botany, Faculty of Science, Ege University, Izmir, Turkey.

3.3. Extraction and isolation

The air-dried and grounded aerial parts of plant (620 g) were extracted with methanol (MeOH) (30%) (2.6 L) for 8 h, under reflux. After filtration, the solvent was evaporated under reduced pressure to dryness, and yielded 14.75 g extract. The methanolic extract was subjected to open column chromatography using D101 resin (250 g) (H_2O: MeOH, 80:20 to 0:100; 20% decreasing polarity) to give 103 fractions (Fractions A1–A103). Based on the TLC profiles, the flavonoid-rich fractions (Fr.B: A56-79; 637.5 mg) were selected for further purification. Fr. B was chromatographed over silica gel (125 g) using EtOAc:MeOH:H_2O (100:10:5, 750 mL; 100:12.5:7.5, 2530 mL; 100:15:10, 2000 mL; 100:17.5:13.5, 520 mL) to yield 256 fractions. Fractions B13–B24 (25 mg) was separated by Sephadex LH-20 (35 g) using MeOH (100%, 350 mL) to give **5a-5b** as a mixture (4.8 mg). Fractions B28–B44 (35 mg) re-chromatographed over Sephadex LH-20 (35 g) using MeOH (100%, 300 mL) to afford 40 fractions (D). Fractions D20–D40 (28.6 mg) were combined and subjected to Sephadex LH-20 (35 g) using MeOH (100%, 350 mL) to give **4a-4b** as a mixture (13.6 mg). Fractions B51-B59 (13.6 mg) were combined to afford compound **3** (17.3 mg). Fractions B90-B126 (38.6 mg) was purified on Sephadex LH-20 (35 g) using MeOH (100%, 450 mL) to give **2** (17.8 mg). Fractions B157–B198 (54.4 mg) was chromatographed on a silica gel column (40 g) using EtOAc:MeOH:H_2O (100:10:5, 786 mL; 100:20:15, 250 mL) to afford 80 fractions. Fraction G36–G53 (27.2 mg) were combined and re-chromatographed over silica gel column (12 g) using Petroleum ether:$CHCl_3$:MeOH:H_2O (5:60:30:2300 mL; 5:60:40:7.5, 100 mL) to afford **1** (11.1 mg).

3.3.1. Kaempferol-3-O-[2-O-(β-D-xylopyranosyl)-3-O-(β-D-glucopyranosyl)]-α-L-rhamnopyranosyl-7-O-α-L-rhamnopyranoside (1)

Yellow amorphous powder; QTOF-MS: m/z = 895.25803 $[M + Na]^+$ (calcd. for $C_{38}H_{48}O_{23}Na$: 895.24781) (positive mode); $[\alpha]_D^{20}$ −5.17 (*c* 0.0008, H_2O); IR (KBr) ν_{max} 3405, 1657, 1603, 1494, 1451 cm^{-1}; ^1H NMR (Pyridine-d_5, 400 MHz) and ^{13}C NMR (Pyridine-d_5, 100 MHz) data: see Table 1.

3.3.2. Kaempferol-3-O-[2-O-((6-O-trans-p-coumaryl)-β-D-glucopyranosyl)-3-O-(β-D-xylopyranosyl)]-α-L-rhamnopyranosyl-7-O-α-L-rhamnopyranoside (2)

Yellow amorphous powder; QTOF-MS: m/z = 1041.29511 $[M + Na]^+$ (calcd. for $C_{47}H_{54}O_{25}Na$: 1041.284618) (positive mode); $[\alpha]_D^{20}$ −1.63 (*c* 0.001, H_2O); IR (KBr) ν_{max} 3422, 1688, 1655, 1604, 1494, 1451 cm^{-1}; ^1H NMR (Pyridine-d_5, 400 MHz) and ^{13}C NMR (Pyridine-d_5, 100 MHz) data: see Table 1.

3.3.3. Kaempferol-3-O-[2-O-(β-D-xylopyranosyl)]-α-L-rhamnopyranosyl-7-O-α-L-rhamnopyranoside (3)

Yellow amorphous powder; ^1H-NMR (400 MHz, DMSO-d6) data was identical to those reported in the literature (Berrehal et al., 2012).

3.3.4. Kaempferol-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside (4a) and isorhamnetin-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside (4b)

Yellow amorphous powder; **4a** (major) and **4b** (minor) were isolated as a mixture. ^1H-NMR (400 MHz, DMSO-d6) data was identical to those reported in the literature (Berrehal et al., 2012).

3.3.5. Kaempferol-3,7-di-O-α–L-rhamnopyranoside (5a) and isorhamnetin-3,7-di-O-α-L-rhamnopyranoside (5b)

Yellow amorphous powder; **5a** (major) and **5b** (minor) were isolated as a mixture. ^1H-NMR (400 MHz, DMSO-d6) data was identical to those reported in the literature (Berrehal et al., 2012).

3.4. Acid hydrolysis

The crude flavonoid mixture of fraction B199-233 (68.8 mg) was heated at 60 °C with 1:1 0.5 N H_2SO_4-dioxane (3 mL) for 2 h, and then evaporated in vacuo. The solution was partitioned with EtOAc, and the H_2O layer was neutralized with 0.5 M NaOH. After gaining the hydrolyzed mixture, two monosaccharides were purified utilizing normal-phase silica gel as stationary phase (20 × 120 mm, 20 g) eluting with $CHCl_3$:MeOH:H_2O solvent system (70:30:3; 61:32:7; 60:40:10). After purification, the obtained sugar units were identified by comparison with authentic samples using TLC in *n*-BuOH:CH_3COOH:H_2O (4:1:5) system and their identity was confirmed after preparative TLC in the same solvent. The optical rotation of each purified sugar was measured to afford L-rhamnose ($[\alpha]_D^{20}$ +40.0, *c* 0.005, H_2O) and D-glucose ($[\alpha]_D^{20}$ +13.15, *c* 0.011, H_2O). The chromatographic separation studies yielded insufficient amount of xylose to obtain its optical rotation. As xylose derives from glucose via oxidation of C-6 followed by decarboxylation, its absolute configuration was directly suggested to be D based on the biosynthetic foundation.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phytol.2019.01.027.

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