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NOTE

A new flavonol galloylrhamnoside and a new lignan glucoside from the leaves of *Koelreuteria henryi* Dummer

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Abstract A new flavonol galloylrhamnoside, kaempferol 3-*O*-(2″,3″-di-*O*-galloyl)-α-L-rhamnopyranoside, and a new lignan glycoside, hinokinin 7-*O*-*β*-D-glucopyranoside were isolated from the leaves of *Koelreuteria henryi*, along with 18 known compounds, including six flavonol glycosides (**3**–**8**), three lignans (**9**–**11**), four chlorophyll derivatives (**12**–**15**), two steroids (**16**, **17**), and three aromatic compounds (**18**–**20**). The structures were determined on the basis of spectral analysis and chemical evidence. The scavenging effect of **1**–**8** and **20** on the stable free radical 1,1-diphenyl-2-picrylhydrazyl was examined. Compounds **1**, **5**, **6**, and **20** showed more potent activity than that of trolox.

Keywords *Koelreuteria henryi* · Sapindaceae · Flavonol galloylrhamnoside · Lignan glycoside · Radical-scavenging effect

Introduction

Koelreuteria henryi Dummer (Sapindaceae), a deciduous tree indigenous to Taiwan, is widely distributed in broad-leaf forests at altitudes below 1,000 m throughout this island [1]. Its roots, bark, twigs, and leaves have been used in traditional folk medicine as an antidiarrhea agent and are also used for the treatment of malaria and urethritis [2]. Previous phytochemical studies of this species had led to the isolation of two flavonol glycosides [3] and three cyclolignans [4], and cyclolignans were found to exhibit significant anti-proliferation activity against three cancer cell lines A-549 (lung cancer), MCF-7 (breast cancer), and HT-29 (colon cancer) [4]. However, the leaves may not have been fully investigated, and there may still exist many other bioactive constituents worth being studied phytochemically. In the course of our studies on natural antioxidants, we examined the constituents of the acetone extract of the leaves of *K. henryi*. The present paper describes the isolation and structural elucidation of a new flavonol galloylrhamnoside, kaempferol 3-*O*-(2″,3″-di-*O*-galloyl)-α-L-rhamnopyranoside (**1**), and a new lignan glycoside, hinokinin 7-*O*-*β*-D-glucopyranoside (**2**) along with six flavonol glycosides (**3**–**8**), three lignans (**9**–**11**), four chlorophyll derivatives (**12**–**15**), two steroids (**16**, **17**), and three aromatic compounds (**18**–**20**) from the acetone extract, as well as the radical-scavenging effect of **1**–**8** and **20** (Fig. 1).

Results and discussion

The acetone extract of the leaves of the plant was partitioned as described in the "Experimental" to give three fractions soluble in ethyl acetate, *n*-BuOH, and H_2O. The EtOAc-soluble fraction was subjected to a combination of silica gel and HPLC with various solvent systems to afford **1**–**20**. Compounds **3**–**20** were identified as kaempferol 3-*O*-*β*-D-glucopyranoside (**3**) [5], kaempferol 3-*O*-α-L-arabinopyranoside (**4**) [6], quercetin 3-*O*-α-L-arabinopyranoside (**5**) [7], quercetin 3-*O*-*β*-D-glucopyranoside (**6**) [5], quercetin 3-*O*-*β*-D-galactopyranoside (**7**) [8], apigenin 4′-*O*-*β*-D-glucopyranoside (**8**) [9], austrobailignan-1 (**9**) [4], austrobailignan-2 (**10**) [4], (+)-sesamin (**11**) [10], pheophorbide a (**12**) [11], pheophorbide b (**13**) [11], methyl

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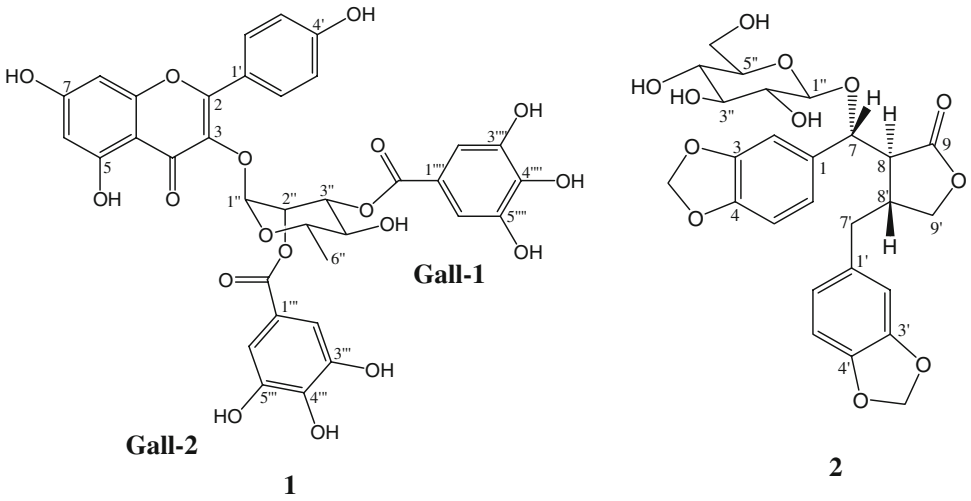
Fig. 1 Structures of new compounds **1** and **2**



pheophorbide a (**14**) [11], methyl pheophorbide b (**15**) [11], β-sitosterol (**16**) [12], β-stigmasterol (**17**) [12], α-tocopherol (**18**) [13], α-tocopheryl quinone (**19**) [14], methyl gallate (**20**) [15] based on their physical and spectral data.

Compound **1** was obtained as an amorphous powder, and its molecular formula was determined to be $C_{35}H_{28}O_{18}$, as deduced from an $[M + Na]^+$ ion at *m/z* 759.1143 in the HR-FAB-MS and ^{13}C-NMR data. Its IR spectrum indicated the presence of a hydroxyl group (3,363 cm^{-1}), an ester carbonyl group (1,719 cm^{-1}), and a benzene ring (1,612, 1,506 cm^{-1}). Its UV spectrum exhibited absorption maxima at 269 and 341 nm. The structure of **1** was established by ^{1}H- and ^{13}C-NMR (Table 1) and 2D-NMR data. In the ^{1}H-NMR spectrum of **1** displayed the characteristic signals of the kaempferol nucleus [5]: two doublets at δ_H 6.20 (1H, d, $J = 1.8$ Hz) and 6.40 (1H, d, $J = 1.8$ Hz), assigned to the H-6 and H-8 protons, respectively, and a pair of AA′XX′ phenyl protons at δ_H 6.98 (2H, d, $J = 8.5$ Hz) and 7.88 (2H, d, $J = 8.5$ Hz), assigned to H-3′, H-5′, and H-2′, H-6′, respectively. As to the sugar protons' region of the ^{1}H-NMR spectrum, there were signals for an anomeric proton at δ_H 5.62 (1H, br s, H-1″), four methine protons at δ_H 3.72 (1H, t, $J = 9.8$ Hz, H-4″), 5.38 (1H, dd, $J = 3.0$, 9.8 Hz, H-3″), 5.88 (1H, t, $J = 3.0$ Hz, H-2″), and a secondary methyl functionality at δ_H 1.07 (3H, d, $J = 6.1$ Hz, H-6″), suggesting the presence of an rhamnopyranoside [6]. In the HMBC spectrum, the rhamnose H-1 signal at δ_H 5.62 correlated with the C-3 resonance of kaempferol at δ_C 135.5 through a ^3J coupling, suggesting that the sugar unit was located at the C-3 position. The ^{13}C-NMR resonances of the glycoside moiety coincided well with those of kaempferol 3-*O*-rhamnopyranoside. These data, coupled with the FAB-MS data, suggested that **1** is a digallate of kaempferol 3-*O*-rhamnopyranoside. The two galloyl groups were attached to C-2 and C-3 of the rhamnopyranosyl residue based on the remarkable downfield shifts of the H-2″ (δ_H 5.88) and H-3″ (δ_H 5.38) signals, and they were further confirmed by HMBC measurements (Fig. 2). The absolute configuration of the rhamnose was determined to be L-rhamnose by its NMR data and the optical rotation [16] after acidic hydrolysis of **1**. Based on the above findings and comparison with the analog of **1** [17], the structure of compound **1** has been elucidated as kaempferol 3-*O*-(2,3-di-*O*-galloyl)-α-L-rhamnopyranoside.

Compound **2** was obtained as an amorphous white powder. Its molecular formula $C_{26}H_{28}O_{12}$ was deduced from an $[M + H]^+$ ion at *m/z* 533.1635 in the HR-FAB-MS. Analysis of the IR spectrum of **2** indicated the presence of a hydroxyl group (3,366 cm^{-1}) and a γ-lactone carbonyl (1,760 cm^{-1}). The ^{1}H-NMR spectrum (Table 1) showed that **2** has two methylenedioxy groups [δ_H 5.88 (1H, s), 5.89 (1H, s); δ_H 5.93 (2H, s)] attached to phenyl functionalities and two sets of ABX type 1,3,4-trisubstituted phenyl protons [δ_H 6.76 (1H, d, $J = 8.1$ Hz, H-5), 6.85 (1H, dd, $J = 1.3$, 8.1 Hz, H-6), 6.91 (1H, d, $J = 1.3$ Hz, H-2); δ_H 6.57 (1H, dd, $J = 1.4$, 7.5 Hz, H-6′), 6.60 (1H, d, $J = 1.4$ Hz, H-2′), 6.70 (1H, d, $J = 7.5$ Hz, H-5′)] at the lower field. The signals of sugar unit were at δ_H 3.17 (1H, m, H-5″), 3.28 (1H, t, $J = 7.5$, H-2″), 3.29 (1H, t, $J = 7.5$ Hz, H-4″), 3.34 (1H, t, $J = 7.5$ Hz, H-3″), 3.58 (1H, dd, $J = 5.4$, 11.9 Hz, H-6″a), 3.70 (1H, dd, $J = 2.3$, 11.9 Hz, H-6″b), and 4.41 (1H, d, $J = 7.5$ Hz, H-1″), suggesting the presence of a glucopyranoside [6]. The relatively large J value (7.5 Hz) of the anomeric proton at δ_H 4.41 indicated a β-configuration for the glucopyranosyl moiety. The absolute configuration of the glucose was determined to be D-glucose by the optical rotation compared with authentic sample after acidic hydrolysis of **2**.

All of the above data coupled with ^{13}C-NMR assignments (Table 1) were compatible with those of hinokinin [7], except that a glucopyranoside was attached at C-7, as further evidenced from a cross peak between H-1″ (δ_H

Table 1 ^{1}H- and ^{13}C-NMR data for **1** and **2** (^{1}H; 500 MHz, ^{13}C; 125 MHz, CD_3OD)

	1			**2**	
	^{13}C	^{1}H		^{13}C	^{1}H
1			1	148.8	
2	159.1		2	108.6	6.91 (d, 1.3)
3	135.5		3	149.0	
4	179.5		4	134.3	
5	163.2		5	108.7	6.76 (d, 8.1)
6	99.9	6.20 (d, 1.8)	6	121.6	6.85 (d, 1.3, 8.1)
7	165.9		7	80.9	5.10 (d, 4.8)
8	94.8	6.40 (d, 1.8)	8	52.0	3.01 (dd, 4.8, 7.3)
1′	122.4		9	179.1	
2′	110.4	7.88 (d, 8.5)	1′	147.7	
3′	146.5	6.98 (d, 8.5)	2′	110.1	6.60 (d, 1.4)
4′	161.7		3′	149.3	
5′	146.5	6.98 (d, 8.5)	4′	133.8	
6′	110.4	7.88 (d, 8.5)	5′	109.2	6.70 (d, 7.5)
Rha			6′	122.6	6.57 (dd, 1.4, 7.5)
1″	100.3	5.62 (br*s*)	7′	39.4	2.81 (dd, 5.5,13.6)
					2.53 (dd, 9.3,13.6)
2″	71.0	5.88 (t, 3.0)	8′	40.3	2.60–2.66 (m)
3″	73.3	5.38 (dd, 3.0, 9.8)	9′	72.8	3.89 (d, 7.2)
4″	71.2	3.72 (t, 9.8)	Glc		
5″	72.4	3.54–3.60 (m)	1″	103.7	4.41 (d, 7.5)
6″	17.9	1.07 (d, 6.1)	2″	75.5	3.28 (t, 7.5)
Gall-1			3″	78.1	3.34 (t, 7.5)
1‴	120.8		4″	71.4	3.29 (t, 7.5)
2‴	110.4	6.99 (s)	5″	78.0	3.17 (m)
3‴	146.6		6″	62.6	3.58 (dd, 5.4,11.9)
					3.70 (dd, 2.3,11.9)
4‴	140.2		–O–CH_2–O–	102.2	5.88 (s)
					5.89 (s)
5‴	146.6		–O–CH_2–O–	102.5	5.93 (s)
6‴	110.4	7.03 (s)			
C=O	166.8				
Gall-2					
1⁗	121.3	6.99 (s)			
2⁗	110.4				
3⁗	146.3				
4⁗	139.9				
5⁗	146.3				
6⁗	110.4	7.03 (s)			
C=O	167.9				

Coupling constants (J in Hz) are given in parentheses

4.41) and C-7 (δ_C 80.9) through a three-bond coupling in the HMBC experiment. The relative configurations of both H-7/H-8 and H-8/H-8′ were determined as *trans* form, the same as those of hinokinin, as deduced from the observation of key cross peaks, including H-7 (δ_H 5.10)/H-8 (δ_H 3.10) and H-7 (δ_H 5.10)/H-8′ (δ_H 2.63), and a lack of correlation between H-8 and H-8′ in the NOESY experiment. Accordingly, **2** was concluded to be hinokinin 7-*O*-*β*-D-glucopyranoside.

As far as we know, this is the first example of the isolation of **3**–**20**, except **4**, **9**, and **10**, from *K. henryi* and, further, **1** and **2** are believed to be new compounds.

The scavenging effect of phenolic compounds (**1**–**8**, **16**, and **17**) on the stable free radical 1,1-diphenyl-2-

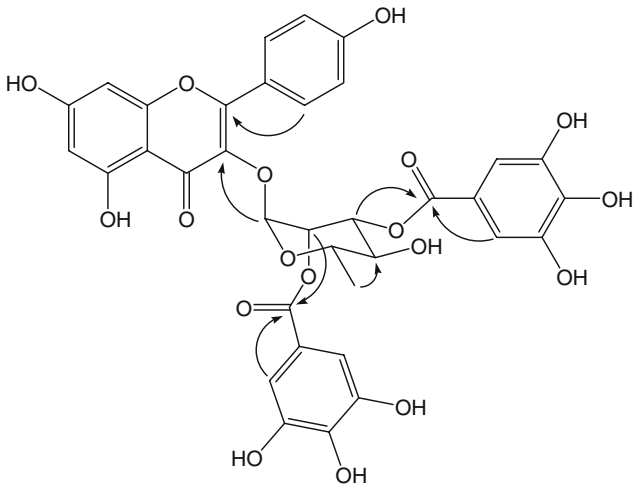


Fig. 2 Key HMBC correlations of **1**

Table 2 DPPH radical-scavenging activity of phenolic compounds **1**–**8**, **16** and **20**

Compounds	IC_{50} (μM)
Kaempferol 3-*O*-(2,3-di-*O*-galloyl)-α-rhamnopyranoside (**1**)	3.6 ± 1.2
Hinokinin 7-*O*-β-D-glucopyranoside (**2**)	>100
Kaempferol 3-*O*-β-D-glucopyranoside (**3**)	>100
Kaempferol 3-*O*-α-L-arabinopyranoside (**4**)	>100
Quercetin 3-*O*-α-L-arabinopyranoside (**5**)	15.6 ± 2.5
Quercetin 3-*O*-β-D-glucopyranoside (**6**)	12.2 ± 1.8
Quercetin 3-*O*-β-D-galactopyranoside (**7**)	29.5 ± 3.5
Apigenin 4′-*O*-β-D-glucopyranoside (**8**)	>100
Methyl gallate (**20**)	12.2 ± 2.1
Trolox[a]	22.1 ± 1.9

[a] Positive control used in this study

picrylhydrazyl (DPPH) was examined, and the activity was compared with that of the standard antioxidant trolox (Table 2). It was shown that chemical entities with catechol or pyrogallol functionalities would exhibit strong antioxidant activities [18]. This was also observed in **1**, **5**–**7**, and **20**, which possessed at least one catechol group or pyrogallol group in their structures, and exhibited significant DPPH radical-scavenging activity with respective IC_{50} values of 3.6, 15.6, 12.2, 29.5, and 12.2 μM when compared with the positive control, trolox (IC_{50} = 22.1 μM).

Experimental

General

Optical rotations were performed with a JASCO DIP-1000 digital polarimeter. FT-IR spectra were recorded on a Thermo Mattson IR-300 spectrophotometer. UV spectra were measured with Shimadzu UV-1601PC. MS were recorded on a VG Platform Electrospray and JEOL SX-102 mass spectrometers. ^{1}H- and ^{13}C-NMR spectra were recorded with Bruker DRX-500 spectrometer (^{1}H, 500 MHz; ^{13}C, 125 MHz), and chemical shifts were given on a δ (ppm) scale with tetramethylsilane (TMS) as an internal standard. Silica gel Kieselgel 60 (70–230 mesh; Merck) was used for column chromatography (CC). HPLC separation was run on a Hitachi L-7000 series. For HPLC column chromatography, Merck LiChrospher *Si* (7 μm, 250 × 10 mm i.d.) was used.

Plant material

The leaves of *K. henryi* Dummer were collected in Taipei, Taiwan, in August 2005, and identified by Mr. Nien-yung Chiu, a technician of the Institute of Chinese Pharmaceutical Science, China Medical University. A voucher specimen was deposited at Taipei Medical University, Taipei, Taiwan.

Extraction and isolation

The fresh leaves of *K. henryi* (3.1 kg) were extracted with Me_2CO (15 l) at room temperature three times and the solvent was removed under reduced pressure to give a brown syrup (320 g). This extract was suspended in H_2O (1 l × 3), and the suspension was extracted with EtOAc (1 l × 3) and *n*-BuOH (1 l × 3), respectively. The EtOAc layer gave a residue (160 g) on evaporation in vacuo, which was absorbed on 200 g of SiO_2, and then subjected to CC (550 g SiO_2; hexane/AcOEt gradient) to afford seven fractions: Fr. 1 (hexane/AcOEt 96:4; 2,000 ml); Fr. 2 (hexane/AcOEt 85:15; 2,000 ml); Fr. 3 (hexane/AcOEt 80:20; 2,100 ml); Fr. 4 (hexane/AcOEt 75:25; 1,000 ml); Fr. 5 (hexane/AcOEt 40:60; 1,600 ml); Fr. 6 (hexane/AcOEt 20:80; 2,000 ml), and Fr. 7 (AcOEt 2,600 ml). Repeated purification of Fr. 1 (16.2 g) by CC (SiO_2; hexane/AcOEt 50:1) followed by HPLC purification afforded **18** (24.0 mg). Fr. 2 (8.5 g) was subjected to CC (SiO_2; hexane/Acetone 15:1) followed by HPLC purification, which afforded **11** (7.5 mg), **16** (42.4 mg), **17** (17.5 mg), and **19** (19.5 mg). Fr. 3 (18.4 g) was purified by CC (SiO_2; hexane/AcOEt 5:1) followed by HPLC to afford **9** (17.2 mg) and **15** (14.8 mg). Fr. 4 (5.6 g) was subjected to CC (SiO_2; hexane/AcOEt 4:1) followed by HPLC to afford

10 (13.5 mg) and **14** (12.2 mg). Fr. 5 (25.0 g) was purified by CC (SiO_2; hexane/AcOEt 2:3) followed by HPLC purification, which afforded **12** (22.3 mg) and **13** (11.1 mg). Fr. 6 (21.9 g) was subjected to CC (SiO_2; hexane/AcOEt 1:3) followed by HPLC purification, which afforded **3** (27.5 mg), **4** (50.4 mg), and **8** (40.5 mg). Fr. 7 (31.1 g) was purified by CC (SiO_2; acetone/MeOH 1:1) followed by HPLC to provide **1** (24.7 mg), **2** (38.5 mg), **5** (35.8 mg), **6** (46.3 mg), **7** (38.5 mg), and **20** (62.5 mg).

The known compounds were identified by direct comparison with authentic samples, comparison of spectral data with those reported, or analyses of NMR spectra.

Kaempferol 3-*O*-(2,3-di-*O*-galloyl)-α-L-rhamnopyranoside (**1**)

Yellow amorphous powder

$[\alpha]_D^{19}$ +11.3° (*c* 1.0, MeOH). UV (MeOH) λ_{max} (log ε): 341 (4.37), 269 (4.91). IR ν_{max} cm^{-1}: 3,363, 1,719, 1,652, 1,612, 1,506, 1,449, 1,360, 1,207, 1,178, 1,035, 971, 764. ^1H- and ^{13}C-NMR: see Table 1. HR-FAB-MS (pos.): 759.1143 ($[M + Na]^+$, $C_{35}H_{28}O_{18}Na^+$; calc. 759.1173).

Hinokinin 7-*O*-β-D-glucopyranoside (**2**)

White amorphous powder

$[\alpha]_D^{21}$ +16.0° (*c* 0.88, MeOH). UV (MeOH) λ_{max} (log ε): 286 (3.50), 236 (3.52). IR ν_{max} cm^{-1}: 3,366, 1,760, 1,489, 1,445, 1,248, 1,037. ^1H- and ^{13}C-NMR: see Table 1. HR-FAB-MS (pos.): 533.1635 $[M + H]^+$, $C_{26}H_{29}O_{12}^+$; calc. 533.1659).

Acidic hydrolysis of **1** and **2**

Compounds **1** (2 mg) and **2** (2 mg) were treated with 0.5 M methanolic HCl at 80°C for 16 h to give methyl glycoside derivatives. Free hydroxyl groups were trimethylsilylated using the Sylon HTP trimethylsilylation reagent (Supelco, Bellefonte, PA) for 20 min at room temperature. After removal of the excess reagent and organic solvent by condensation, the resulting volatile derivatives were dissolved in *n*-hexane, and this solution was used for GC/MS analysis. GC/MS analysis of the trimethylsilylated derivatives was performed on a fused silica capillary column using a temperature gradient of 60–140°C at 25°C min^{-1}, increased to 250°C at 5°C min^{-1}, and then increased to 300°C at 10°C min^{-1}. Several authentic monosaccharides, including arabinose, rhamnose, fructose, xylose, mannose, galactose, and glucose were used as the standards, and arabitol was used as the internal standard. When compared with the trimethylsilylated derivatives of the standards, the monosaccharide composition of **1** and **2** was confirmed to be rhamnose and glucose, respectively. The retention times of the trimethylsilyl methyl rhamnosides were found to be 10.63 and 10.85 min. The retention times of the trimethylsilyl methyl glucosides were found to be 16.22 and 16.55 min.

Determination of aldose configuration

Compound **1** (5 mg) was hydrolyzed by 1 M H_2SO_4 (2 ml) at room temperature overnight. The reaction mixture was then partitioned with EtOAc (3 ml). The aqueous layer was neutralized using 1 M $Ba(OH)_2$ (2 ml) and filtered with glass wool, and was purified by chromatography on Sephadex LH-20 eluted with MeOH to give L-rhamnose: $[\alpha]_D^{23}$ −7.8° (*c* 0.6, H_2O); ^{13}C NMR (pyridine-*d*5) 95.3 (C-1), 74.2 (C-2), 73.2 (C-3), 74.5 (C-4), 70.0 (C-5), 18.9 (C-6).

Compound **2** (3 mg) was hydrolyzed in the same manner as described for **1** to afford D-glucose: $[\alpha]_D^{23}$ +42.7° (*c* 1.0, H_2O).

Assay of scavenging effect on DPPH

The scavenging activity of compounds **1–8** and **20** against DPPH radical was measured according to the method of Kim et al. [19] with slight modification. Each sample was dissolved in MeOH to the final concentration of 2 mg ml^{-1} as stock solutions. Each 20-μl sample solution (50–120 μM) was added to 130 μl of MeOH, and then mixed with 50 μl of 0.6 mM DPPH in methanol for 30 min under light protection at room temperature. The decrease of absorbance resulting from the addition of test compounds was measured at 517 nm using a microplate spectrophotometer (SpectraMax Plus384, Molecular Devices, CA). Trolox was used as the standard sample.

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