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Chemical Constituents from the Roots of *Rehmannia glutinosa*

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Abstract: Ten secondary metabolites, including one new monoterpene rhamnoside (**1**), five terpenoids (**2**–**6**), two nucleosides (**7**–**8**), and two phenylethanoid glycosides (**9**–**10**) were isolated from the roots of *Rehmannia glutinosa*. Their structures were determined by spectroscopic analysis such as NMR and HR-ESI-MS. In the tyrosinase inhibitory assay, compounds **2**, **6** and **8** showed inhibition against tyrosinase. Compounds **1**, **4**, **5**, **6**, **9** and **10** are being reported in the genus *Rehmannia* for the first time.

Keywords: *Rehmannia glutinosa*; rhamnoside; phenylethanoid glycoside; tyrosinase.

1. Introduction

Rehmannia glutinosa (Dihuang) is a widely used traditional Chinese herb belonging to Scrophulariaceae family, and mainly distributed in Henan, Liaoning, Shandong, Gansu, Jiangsu, Hebei, Shaanxi and Shanxi Provinces [1]. *R. glutinosa* was listed as a "top grade" herb in China and recorded in Chinese medical classics "Shennong's Herba" [2]. Its dried roots, also called as "Sheng Dihuang", are basically thought as a drug for nourishing *Yin* (which means negative, dark, and feminine in traditional Chinese medicine) and to tonify the kidney, indicating that *R. glutinosa* has various pharmacological effects and phytochemical compositions [3]. In the past decades, plenty of chemical and pharmacological studies have been conducted on *R. glutinosa*. More than 200 compounds have been isolated from the herb [4], including iridoids [5-7], ionones [8-9], phenylethanoid glycosides [10-11] and others. Its extract and chemical constituents were reported to possess wide pharmacological actions on the blood, immune, endocrine, cardiovascular and nervous systems [12]. With the development of innovative methods for separation, structure analysis, pharmacological evaluation, more and more chemical components in *R. glutinosa* have been discovered, and its pharmacological actions have been further improved by development [13-14]. However, till now little attention has been paid on its

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tyrosinase inhibitory activities and corresponding phytochemical constituents [15-16]. In our continuing exploration of novel tyrosinase inhibitors from natural products [17-19], the ethanolic extract of *R. glutinosa* roots was found to show potential tyrosinase inhibitory activity. Further research resulted in the isolation and structure elucidation of a new rhamnoside of long-chain fatty alcohol (**1**) and nine known compounds (**2**–**10**). Compounds **2**, **6** and **8** showed obvious tyrosinase inhibitory activities.

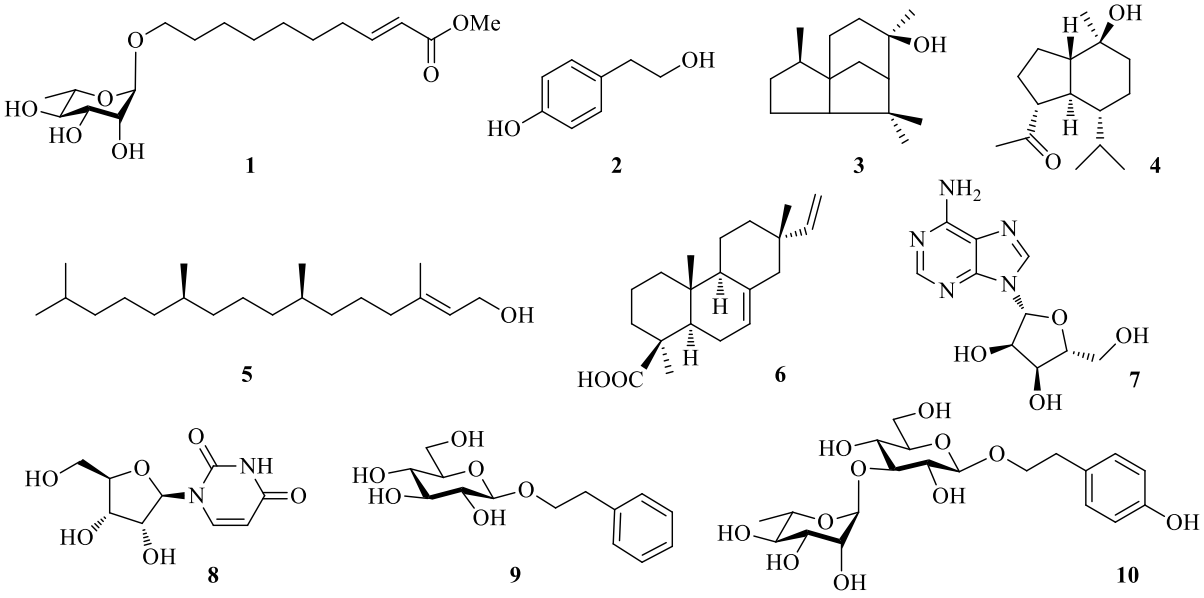

Figure 1. Structures of compounds **1**–**10** isolated from *R. glutinosa* roots

2. Materials and Methods

2.1. General Experimental Procedures

HR-ESI-MS and NMR spectra were measured on a Waters Xevo G2-XS QTof spectrometer, a Bruker AM-400 spectrometer, respectively. Column chromatography (CC) was performed on silica gel, ODS (50 μm, Fuji Silysia Chemical Ltd., Japan), Sephadex LH-20 (GE health care Bio-Sciences AB, Sweden) and high performance liquid chromatography (Agilent 1200).

2.2. Plant Materials

The fresh *R. glutinosa* roots were collected in Jiaozuo City, Henan Province, China, and identified by Lin Yang (Associate Professor, Lanzhou University of Technology). A voucher specimen (SPH2021K) was stored in Food and Pharmacy College, Xuchang University.

2.3. Extraction and Isolation

The air-dried *R. glutinosa* roots (2.5 kg) were powdered and extracted with 95% ethanol (5d × 3 × 12 L) under room temperature. The combined extracts were evaporated under reduced pressure to give a crude extract (51.7 g), which was further graded on a silica gel CC (CH_2Cl_2-MeOH, 100:0 to 2:1) to give ten fractions F1-F10. Fractions F5-F9 were purified by open silica gel CC/ODS CC/semipreparative HPLC to yield compounds **1**–**10**.

Fraction F5 (2.3 g) was subjected to Sephadex LH20 chromatography with CH_2Cl_2 as the eluent to yield four subfractions (F5-1−F5-4). Compounds **5** (17.1 mg) and **2** (10.5 mg) were purified by a Sephadex LH-20 CC (CH_2Cl_2) from F5-1 and F5-2, respectively. Subfraction F5-3 was passed on a silica gel CC (CH_2Cl_2-MeOH, 60:1 to 50:1) to give compound **3** (9.4 mg). Fraction F6 (1.8 g) was divided to four subfractions (F6-1–F6-4) by a silica gel CC (CH_2Cl_2-MeOH, 50:1 to 20:1). F6-3 was

separated on a Sephadex LH-20 CC (CH_2Cl_2-MeOH, 1:1) to obtain **4** (12.5 mg) and **6** (23.8 mg). Fraction F8 (2.1 g) gave five subfractions (F8-1–F8-5) after an ODS CC (MeOH-H_2O, 20:80 to 90:10). F8-1 was further purified on a Sephadex LH-20 CC (MeOH) to yiled **7** (12.7 mg) and **9** (8.1 mg). F8-3 was passed through an ODS CC (MeOH-H_2O, 40:60) to obtain **1** (12.1 mg). Fraction F9 (4.4 g) was eluted by ODS CC (MeOH-H_2O, 10:90 to 80:20) to give subfractions F9-1–F9-4. Compound **10** (16.2 mg) was obtained from F9-1 after purification by Sephadex LH-20 CC (MeOH). F9-4 was passed through an ODS CC (MeOH-H_2O, 30:70) to give **8** (11.9 mg).

*2.4. Acid Hydrolysis of Compound **1***

Compound **1** was hydrolyzed according to the literature procedures [18] to give (*E*)-10-hydroxydec-2-enoic acid methyl ester (**1a**) [20] and L-rhamnose, $[\alpha]_D^{20}$+1.9° (c 0.1, H_2O) [reported: $[\alpha]_D^{20}$+2.4° (c 1, H_2O)] [21].

*(E)-10-hydroxydec-2-enoic acid methyl ester (**1a**)*. Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.01 (1H, dt, *J* = 15.6, 8.0 Hz, H-3), 5.86 (1H, d, *J* = 15.6 Hz, H-2), 4.25-4.14 (2H, m, H-10), 3.73 (3H, s, OC*H*$_3$), 2.22 (2H, m, H-4), 1.73 (2H, m, H-9), 1.47-1.33 (8H, m, H-5, H-6, H-7, H-8). ^{13}C NMR ($CDCl_3$, 100 MHz): δc 168.9 (C-1), 151.3 (C-3), 120.4 (C-2), 71.9 (C-10), 52.2 (OC*H*$_3$), 32.2 (C-4), 28.7 (C-9), 28.6 (C-7), 28.6 (C-6), 27.6 (C-5), 25.2 (C-8).

2.5. Mushroom Tyrosinase Inhibition Assay

Mushroom tyrosinase inhibition assay was performed according to the literature procedures [19], using arbutin as the positive control. All experiments were repeated three times. The %inhibition was calculated by (Ac − As)/Ac × 100

Where, As is the absorbance of tested compound and Ac the non-treated control. The results were analyzed by program GraphPad Prism 5.0. Data are expressed as means ± SEMs of triplicate.

3. Results and Discussion

3.1. Isolation and Structure Elucidation

Compounds **1**–**10** were isolated and purified from the *R. glutinosa* roots by various chromatographic techniques. Their structures were identified by spectral data and physiochemical properties as (*E*)-10-hydroxydec-2-enoic acid methyl ester 10-O-*α*-L-rhamnoside (**1**), tyrosol (**2**) [22], cedrol (**3**) [23], ent-oplopanone (**4**) [24], *E*-phytol (**5**) [25], 4-*epi*-*iso*pimaric acid (**6**) [26], adenosine (**7**) [27], uridine (**8**) [28], 2-phenylethyl-*β*-D-glucoside (**9**) [29], cistanoside G (**10**) [30], respectively, by comparison of spectral data in the literatures. Compounds **1**, **4**, **5**, **6**, **9** and **10** were for the first time isolated from genus *Rehmannia*, which would enrich our knowledge about phytochemical constituents of *R. glutinosa*.

The molecular formula of **1** was found to be $C_{17}H_{30}O_7$ based on HR-ESI-MS which corresponds to three degrees of unsaturation. Strong absorption bands at 3407 and 1720 cm^{-1} in the IR spectrum revealed the presence of hydroxy and carbonyl groups. The ^{13}C NMR spectrum of **1** showed seventeen carbons. When combined with its DEPT-135 spectrum, these carbons could be classified into one carbonyl, two olefinic carbons (sp^2 methine carbon), five sp^3 oxygenated methine carbons, seven sp^3 methylene carbons (including one oxygenated carbon), one methyl carbon, and one methoxyl group. The ^{1}H NMR spectrum showed that **1** has two olefinic protons, five oxygenated methine protons, seven sp^3 methylene carbons, one methyl protons, and one methoxyl protons, which were associated with the directly attached carbon atoms in the HSQC experiment. The ^{1}H-^{1}H COSY experiment and the coupling values of the protons indicated the presence of two spin systems [H-2−H-3−H-4−H-5−H-6−H-7−H-8−H-9−H-10, H-1′−H-2′−H-3′−H-4′−H-5′−H-6′]. Combined with its molecular formula, degrees of unsaturation, and deduced spin systems, the key HMBC correlations shown in Figure 2 were used to build up the structure of **1** as (*E*)-10-hydroxydec-2-enoic acid methyl ester 10-O-*α*-L-rhamnoside. The anomeric proton at δ_H 4.74 (1H, d, *J* = 1.2 Hz, H-1′), and ^{13}C NMR data (δ_C 99.9, 73.2, 72.1, 71.3, 68.2,

17.7) indicated the sugar moiety was α-rhamnopyranoside [31]. Acid hydrolysis of **1** afforded (*E*)-10-hydroxydec-2-enoic acid methyl ester (**1a**) [20] and L-rhamnose. The aglycon **1a** was identified by NMR, and the L-conformation of the rhamnose was confirmed by rotation, $[\alpha]_D^{20}$+1.9° (c 0.1, H_2O) [reported: $[\alpha]_D^{20}$+2.4° (c 1, H_2O)] [21].

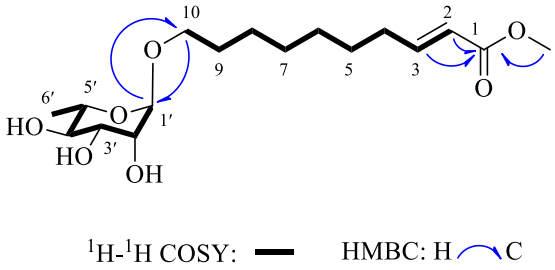

Figure 2. Key ^{1}H-^{1}H COSY and HMBC correlations for compound **1**

*(E)-10-Hydroxydec-2-enoic acid methyl ester 10-O-α-L-rhamnoside (**1**)*:Colorless syrup. $[\alpha]_D^{20}$–12.6° (c 0.33, $CHCl_3$). IR (KBr) ν_{max} 3407, 2927, 2854, 1720, 1272, 1052 cm^{-1}. UV λ_{max} ($CHCl_3$) nm (log ε): 241 (4.72). HR-ESI-MS *m/z* 347.2061 [M + H] $^+$ (calcd for $C_{17}H_{31}O_7$, 347.2070, –2.6 PPM). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 6.97 (1H, dt, *J* = 15.6, 6.8 Hz, H-3), 5.82 (1H, dt, *J* = 15.6, 1.6 Hz, H-2), 4.74 (1H, d, *J* = 1.2 Hz, H-1´), 3.91 (1H, dd, *J* = 3.2, 1.2 Hz, H-2´), 3.76 (1H, dd, *J* = 3.2, 9.6 Hz, H-3´), 3.73 (3H, s, OC*H*$_3$), 3.66 (1H, dq, *J* = 9.6, 6.0 Hz, H-5´), 3.62 (1H, m, H-10a), 3.47 (1H, t, *J* = 9.6 Hz, H-4´), 3.38 (1H, dt, *J* = 9.2, 2.1 Hz, H-10b), 2.20 (2H, m, H-4), 1.54 (2H, m, H-9), 1.45 (2H, m, H-5), 1.33-1.29 (6H, m, H-6, H-7, H-8), 1.29 (3H, d, *J* = 6.0 Hz, H-6´). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ*c 167.5 (C-1), 150.0 (C-3), 121.1 (C-2), 99.9 (C-1´), 73.2 (C-4´), 72.1 (C-3´), 71.3 (C-2´), 68.2 (C-5´), 67.9 (C-10), 51.6 (O*C*H$_3$), 32.3 (C-4), 29.5 (C-9), 29.3 (C-7), 29.2 (C-6), 28.1 (C-5), 26.2 (C-8), 17.7 (C-6´).

*Tyrosol (**2**)*:Colorless amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.03 (2H, d, *J* = 8.8 Hz, H-2, H-6), 6.72 (2H, d, *J* = 8.4 Hz, H-3, H-5), 4.88 (1H, s, OH), 3.76 (2H, m, H-8), 2.73 (2H, t, *J* = 6.4 Hz, H-7). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ*c 154.5 (C-4), 130.7 (C-1), 130.4 (C-2, C-6), 115.7 (C-3, C-5), 64.1 (C-8), 38.5 (C-7) [22].

*Cedrol (**3**)*: Colorless powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 1.07 (3H, s, H-13), 1.05 (3H, s, H-15), 0.97 (3H, s, H-12), 0.92 (3H, s, H-14). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ*c 75.1 (C-3), 61.1 (C-2), 56.5 (C-10), 54.1 (C-6), 43.4 (C-11), 42.0 (C-1), 41.5 (C-7), 37.0 (C-8), 35.4 (C-4), 31.6 (C-5), 30.2 (C-15), 28.9 (C-12), 27.7 (C-13), 25.4 (C-9), 15.6 (C-14) [23].

*Ent-oplopanone (**4**)*: White amorphous powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 2.64 (1H, m, H-4), 2.19 (3H, s, H-14), 1.19 (3H, s, H-15), 0.89 (3H, d, *J* = 6.7 Hz, H-11), 0.68 (3H, d, *J* = 6.8 Hz, H-12). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ*c 211.6 (C-5), 72.9 (C-10), 57.0 (C-4), 55.7 (C-6), 49.4 (C-7), 46.7 (C-1), 42.0 (C-2), 29.5 (C-11), 29.4 (C-14), 28.6 (C-3), 25.3 (C-8), 23.0 (C-9), 21.9 (C-13), 20.2 (C-14), 15.6 (C-12) [24].

*E-Phytol (**5**)*: Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.41 (1H, t, *J* = 7.6 Hz, H-2), 4.15 (2H, d, *J* = 6.8 Hz, H-1), 1.99 (2H, t, *J* = 8.0 Hz, H-4), 1.67 (3H, s, H-20), 0.86 (6H, d, *J* = 6.0 Hz, H-16, H-17), 0.84 (6H, d, *J* = 6.4 Hz, H-18, H-19). ^{13}C NMR ($CDCl_3$, 100 MHz): *δ*c 140.3 (C-3), 123.1 (C-2), 59.4 (C-1), 39.9 (C-4), 39.4 (C-14), 37.4 (C-8), 37.4 (C-10), 37.3 (C-12), 36.7 (C-6), 32.8 (C-11), 32.7 (C-7), 28.0 (C-15), 25.1 (C-5), 24.8 (C-13), 24.5 (C-9), 22.7 (C-16), 22.6 (C-17), 19.8 (C-18), 19.7 (C-19), 16.2 (C-20) [25].

*4-epi-isoPimaric acid (**6**)*: White powder. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.81 (1H, dd, *J* = 18.0, 11.2 Hz, H-15), 5.38 (1H, d, *J* = 4.8 Hz, H-7), 4.92 (1H, dd, *J* = 18.0, 1.6 Hz, H-16a), 4.86 (1H, dd, *J* = 10.8,

1.6 Hz, H-16a), 1.25 (3H, s, H-18), 0.86 (3H, s, H-17), 0.78 (3H, s, H-20). ^{13}C NMR ($CDCl_3$, 100 MHz): δc 184.0 (C-19), 150.4 (C-15), 134.7 (C-8), 121.5 (C-7), 109.2 (C-16), 51.7 (C-9), 51.3 (C-5), 46.2 (C-14), 43.8 (C-4), 39.9 (C-9), 38.0 (C-3), 36.9 (C-13), 36.4 (C-12), 35.9 (C-10), 29.2 (C-18), 24.3 (C-6), 21.5 (C-17), 21.0 (C-11), 19.6 (C-2), 14.3 (C-20) [26].

*Adenosine (**7**)*:White powder. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 8.41 (1H, s, H-2), 8.20 (1H, s, H-8), 7.42 (2H, s, 6-NH_2), 5.93 (1H, d, *J* = 6.0, H-1´), 5.50-5.10 (3H, m, 2´-OH, 3´-OH, 5´-OH), 4.67 (1H, d, *J* = 5.6, H-2´), 4.20 (1H, m, H-3´), 4.02 (1H, m, H-4´), 3.73 (1H, dd, *J* = 12.4, 2.8 Hz, H-5´a), 3.60 (1H, dd, *J* = 12.4, 2.0 Hz, H-5´b). ^{13}C NMR (DMSO-d_6, 100 MHz): δc 156.2 (C-6), 152.4 (C-2), 149.1 (C-4), 139.9 (C-8), 119.4 (C-5), 87.9 (C-1´), 85.9 (C-4´), 73.5 (C-2´), 70.7 (C-3´), 61.7 (C-5´) [27].

*Uridine (**8**)*: White powder. ^{1}H NMR (DMSO-d_6, 400 MHz): δ_H 11.32 (1H, s, 1-NH), 7.89 (1H, d, *J* = 8.0 Hz, H-4), 5.78 (1H, d, *J* = 5.6 Hz, H-5), 5.65 (1H, d, *J* = 8.0 Hz, H-3), 5.40 (1H, m, OH), 5.10 (2H, m, OH), 4.01 (1H, m, H-6), 3.97 (1H, m, H-7), 3.82 (1H, m, H-8), 3.60 (1H, m, H-9a), 3.53 (1H, m, H-9b). ^{13}C NMR (DMSO-d_6, 100 MHz): δc 163.2 (C-2), 150.8 (C-1), 140.8 (C-4), 101.8 (C-3), 87.7 (C-5), 84.9 (C-8), 73.6 (C-6), 69.9 (C-7), 60.9 (C-9) [28].

*2-Phenylethyl-β-D-glucoside (**9**)*: White amorphous powder. ^{1}H NMR (CD_3OD, 400 MHz): δ_H 7.24 (5H, m, H-2, H-3, H-4, H-5, H-6), 4.20 (1H, d, *J* = 7.6 Hz, H-1′), 3.98 (1H, dt, *J* = 8.4, 8.0 Hz, H-8a), 3.75 (1H, br d, *J* = 12.0 Hz, H-6a′), 3.65 (1H, dt, *J* = 8.4, 8.4 Hz, H-8a), 3.56 (1H, dd, *J* = 12.0, 5.2 Hz, H-6′b), 3.17-3.12 (3H, m, H-3′, H-4′, H-5′), 3.08 (1H, t, *J* = 8.4, H-2′), 2.84 (2H, m, H-7). ^{13}C NMR (CD_3OD, 100 MHz): δc 138.5 (C-1), 128.5 (C-3, C-5), 127.8 (C-2, C-6), 125.6 (C-4), 102.8 (C-1′), 76.6 (C-5′), 76.4 (C-3′), 73.6 (C-2′), 70.1 (C-8), 70.1 (C-4′), 61.2 (C-6′), 35.7 (C-7) [29].

*Cistanoside G (**10**)*:White powder. ^{1}H NMR (CD_3OD, 400 MHz): δ_H 6.96 (2H, d, *J* = 8.4 Hz, H-2, H-6), 6.59 (2H, d, *J* = 8.0 Hz, H-3, H-5), 5.05 (1H, d, *J* = 1.2 Hz, H-1″), 4.19 (1H, d, *J* = 8.0 Hz, H-1′), 2.73 (2H, m, H-7), 1.14 (3H, d, J = 6.0 Hz, H-6″). ^{13}C NMR (CD_3OD, 100 MHz): δc 156.7 (C-4), 130.8 (C-1), 130.7 (C-2), 116.0 (C-3), 104.1 (C-1′), 102.7 (C-1″), 84.5 (C-3′), 77.8 (C-5′), 75.5 (C-2′), 73.9 (C-4″), 72.3 (C-2″), 72.2 (C-3″), 72.0 (C-8), 70.1 (C-5″), 70.0 (C-4′), 62.6 (C-6′), 36.3 (C-7), 17.8 (C-6″) [30].

3.2. Tyrosinase Inhibitory Activities

At a concentration of 25 μM, using kojic acid as the positive control, compounds **1**–**10** were evaluated for their tyrosinase inhibitory activities. However, only **2**, **7** and **8** showed obvious inhibitory activities, with %inhibition values of 21.66±1.28%, 22.48±2.78%, 10.07±0.99%, respectively, close to that of kojic acid (27.17±1.28%). Tyrosol (**2**) has been reported from varied natural sources [32-33], and has been reported to show strong inhibitory activity against mushroom tyrosinase [34], which fits well with the results of this research. 4-*epi*-*iso*Pimaric acid (**6**), a diterpenoids found in *Caesalpinia furfuracea*, *Illicium jiadifengpi*, *Rabdosia kunmingensis*, was tested to show antiviral activities against Coxsackie virus B2 and B6. However, so far inhibitory activity against tyrosinase has not been reported for **6**. As the first research about tyrosinase inhibitory activities, these results above would be of great instruction to novel tyrosinase inhibitors development and medicinal value utilization of *R. glutinosa*.

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Supporting Information

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