Flavonoids, Phenylethanoids and Phenylpropanoids from *Rhodiola rosea* L. and Their Lipid-Lowering Activities on Receptor 5-HT_{2A}

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Abstract Fifteen compounds, including 11 flavonoids, 2 phenylethanoids and 2 phenylpropanoids, were isolated from the roots of *Rhodiola rosea* L. Among them, quercetin (1) and quercetin-3-O- β -D-glucoside (2) were afforded from the genus *Rhodiola* for the first time. All isolates were evaluated for their agitating activities on receptor 5-HT_{2A} and four compounds (12–15) showed obvious agitating activities, which were probably the main lipid-lowering active components of *R. rosea* L.

Keywords flavonoids, phenylpropanoids, phenylethanoids, *Rhodiola rosea*, lipid-lowering activity, receptor 5-HT_{2A}

Introduction

Obesity, mainly caused by over nutrition and inheritance, can give rise to hypertension, hyperlipidemia and heart diseases, which threatens human health directly or potentially.^[1] Lipid regulation is one of the most effective measures that have been developed to deal with obesity.^[1,2]

Rhodiola rosea L., a medicine-food resource plant that grows primarily in mountainous and arctic regions, is widely used as folk medical systems throughout the eastern Europe and Asia to improve resistance to high altitude sickness, stimulate the nervous system and treat fatigue, psychological stress and depression.^[3] The main active mechanism of its anti-allergenic, anti-inflammatory, anti-depressant, anti-oxidant and lipid-lowering activities revealed by pharmacological studies is improving human immunity and strengthening the human self-regulation systems.^[3–5] Besides, compounds reported from *R. rosea* L. contain flavonoids, monoterpenes, triterpenes, phenolic acids along with the specific components of this plant, phenylethanoids (tyrosol and salidroside) and phenylpropanoids (rosin).^[3,4]

As a member of serotonin (5-HT) receptors, receptor 5-HT_{2A} has been found to mediate a variety of serotonin's physiological functions in both the central and peripheral nervous systems, and its selective agonist is a useful therapeutic approach for certain disorders, including hypertension, hyperlipidemia and obesity.^[5] Additionally, it was reported that high activity of 5-HT_{2A} receptor can reduce appetite and food intake to achieve the purpose of lipid regulation.^[2,5,6]

To clarify the lipid-lowering components of the entitled plant, the bioassay-guided investigation was carried out, which led to isolation of 11 flavonoids (Figure 1), 2 phenylethanoids and 2 phenylpropanoids. Among them, flavones 1–2 were isolated from the *Rhodiola* genus for the first time.

Experimental

General apparatus and chemicals

¹H NMR and ¹³C NMR experiments were performed using

Figure 1 Structures of flavonoids, phenylethanoids and phenylpropanoids isolated from *R. rosea* L.

Avance III-600 NMR spectrometers (Bruker, Bremerhaven, Germany) with tetramethylsilane as the internal standard. Preparative HPLC was carried out on Newstyle^{TM} equipment (NP-7000 pump, NU-3000 detector; Hanbon Sci. & Tech., China) with a dynamic axial compression column (50 mm, Hanbon Sci. & Tech., China) filled with C₁₈ (10 μ m, Agilent, USA). Semi-preparative HPLC was performed on a Newstyle^{TM} (pump: NP-7000 serials, detector: NU-3000 serials) with a reversed-phase (RP) C₁₈ column (9.4 $\times$ 250 mm, 5 μ m). HPLC analysis was recorded on Waters E 2695 Separations Module (2998 PDA detector, Waters, USA) with a C₁₈ column (4.5 $\times$ 250 mm, 5 μ m, Agilent, USA). Absorption values were read with Flex Station 3 Benchtop Multi-Mode Microplate Reader (Molecular Devices, Sunnyvale, California, USA). Serotonin hydrochloride (purity > 99%) was purchased from Alfa Aesar as positive control.

Plant material

The roots of *R. rosea* L. was purchased from the Yuzhou traditional Chinese medicine market (Yuzhou, Henan, China) in January 2018 and identified by Professor Jia-Mei Li in Henan Agricultural University. A voucher specimen (No. 2018-08-21) was deposited in the Jiangsu Key Laboratory of Chiral Pharmaceuticals Biosynthesis, Taizhou University.

Extraction and isolation

The air-dried and powdered root of *R. rosea* L. (1 kg) was extracted with 70% EtOH at room temperature. The extracts were combined, condensed *in vacuo*, filtrated by 500 nm ceramic membrane, and then the filtrate was loaded and partitioned by preparative HPLC to give water soluble fraction, 50% EtOH fraction and 95% EtOH fraction. The 50% EtOH fraction (82 g) with an agonistic rate of 38.1% on the receptor 5-HT_{2A} at the concentration of 1.02 mg/mL was chosen for further isolation following bioassay tests (Table S1 in Supporting Information).

The 50% EtOH fraction (82 g) was subjected to preparative HPLC and eluted with MeOH-H₂O-HAc (20 : 80 : 0.08, 40 : 60 : 0.06, 60 : 40 : 0.04, 80 : 20 : 0.02, V/V/V, each 4 CV) mixtures to afford the fractions Frs.1—4. Fr.1 was further fractionated and purified by repeated preparative HPLC and semi-preparative HPLC to obtain the target compound **4** (13 mg). Fr.2 was divided into four fractions Frs.2.1—2.4 by gradient elution using MeCN-H₂O (20 : 80—35 : 65), then Fr.2-2 was further purified by repeated semi-preparative HPLC for compound **9** (6 mg), and Fr.2-3 was further partitioned to yield compounds **6** (12 mg) and **7** (21 mg). Fr.3 was successively partitioned into eight sub-fractions Frs.3.1—3.8 eluted by MeCN-H₂O (45 : 55—55 : 45), and every sub-fraction was further purified by repeated semi-preparative HPLC for compounds **2** (12 mg), **3** (31 mg), **5** (49 mg), **8** (7 mg), **11** (8 mg), **13** (217 mg), **14** (86 mg) and **15** (69 mg). Fr.4 was purified repeatedly by semi-preparative HPLC to obtain compounds **1** (9 mg), **10** (16 mg) and **12** (142 mg). The purities of all titled compounds were > 98% determined by HPLC.

Agonistic activity assay

HEK293 cell line was cultured with 5% CO₂ at 37 °C in DMEM supplemented with 10% FBS. The cells were seeded in a Matrigel coated 96-well black wall/clear bottom plate following been incubated in CO₂ incubator for 24 h, dyed by HDB Wash Free Fluo-8 Calcium Assay kit at 37 °C in dark for one hour, and then treated with tested compounds and positive drug, respectively. The absorption values were read with Flex Station 3 Benchtop Multi-Mode Microplate Reader at room temperature with excitation wavelength at 485 nm, emission wavelength at 525 nm and emission cut-off at 515 nm. The agonistic rates of the test compounds were calculated by comparing with the positive control serotonin hydrochloride, whose agonistic rate was normalized to 100%.^[7]

Results and Discussion

Investigation on the roots of *R. rosea* L. afforded 15 compounds including 11 flavonoids, 2 phenylethanoids and 2 phenylpropanoids. Among them, flavones **1**—**2** were isolated from the *Rhodiola* genus for the first time. As shown in Figure 1, the structures of these compounds were elucidated by comparing their ¹H NMR and ¹³C NMR spectra with the reported literatures.

Quercetin (**1**).^[8] yellowish powder, C₁₅H₁₀O₇, ¹H NMR (600 MHz, CD₃OD) δ: 7.67 (1H, d, *J* = 2.0 Hz), 7.58 (1H, dd, *J* = 8.5, 2.0 Hz), 6.88 (1H, d, *J* = 8.5 Hz), 6.41 (1H, d, *J* = 1.8 Hz), 6.19 (1H, d, *J* = 1.8 Hz); ¹³C NMR (150 MHz, CD₃OD) δ: 175.7 (s), 163.8 (s), 160.6 (s), 156.1 (s), 147.6 (s), 146.6 (s), 145.0 (s), 135.6 (s), 122.0 (s), 119.8 (d), 115.5 (d), 115.0 (d), 102.8 (s), 98.0 (d), 93.2 (d).

Quercetin-3-O-β-D-glucoside (**2**).^[9] yellow powder, C₂₁H₂₀O₁₂, ¹H NMR (600 MHz, CD₃OD) δ: 7.71 (1H, d, *J* = 2.0 Hz), 7.58 (1H, dd, *J* = 8.4, 2.0 Hz), 6.86 (1H, d, *J* = 8.4 Hz), 6.35 (1H, d, *J* = 1.9 Hz), 6.18 (1H, d, *J* = 1.9 Hz), 5.23 (1H, d, *J* = 7.6 Hz), 3.71 (1H, dd, *J* = 11.9, 2.1 Hz), 3.57 (1H, dd, *J* = 11.9, 5.3

Hz), 3.42—3.48 (2H, m), 3.34—3.37 (1H, m), 3.18—3.23 (1H, m); ¹³C NMR (150 MHz, CD₃OD) δ: 179.2 (s), 166.1 (s), 162.9 (s), 158.9 (s), 158.2 (s), 149.7 (s), 145.8 (s), 135.4 (s), 123.3 (d), 123.1 (s), 117.6 (d), 116.0 (d), 105.5 (s), 104.1 (s), 99.9 (d), 94.5 (d), 78.1 (d), 78.0 (d), 75.6 (d), 71.1 (d), 62.5 (t).

Rutin (**3**).^[10] yellowish powder, C₂₇H₃₀O₁₆, ¹H NMR (600 MHz, CD₃OD) δ: 7.88 (1H, d, *J* = 1.4 Hz), 7.58 (1H, dd, *J* = 8.5, 1.4 Hz), 6.85 (1H, d, *J* = 8.5 Hz), 6.43 (1H, d, *J* = 1.2 Hz), 6.21 (1H, d, *J* = 1.2 Hz), 5.05 (1H, d, *J* = 7.8 Hz), 4.51 (1H, s), 3.31—4.63 (10H, m), 1.15 (3H, d, *J* = 6.6 Hz); ¹³C NMR (150 MHz, CD₃OD) δ: 179.6 (s), 166.1 (s), 163.1 (s), 158.7 (s), 158.4 (s), 150.1 (s), 145.6 (s), 135.6 (s), 122.9 (d), 122.7 (s), 117.8 (d), 116.0 (d), 105.9 (s), 105.3 (s), 101.8 (s), 99.9 (d), 94.5 (d), 75.2 (d), 75.0 (d), 73.8 (d), 73.0 (d), 72.2 (d), 71.8 (d), 70.1 (d), 69.5 (d), 67.2 (t), 18.1 (q).

Herbacetin-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside (**4**).^[11] white powder, C₂₇H₃₀O₁₆, ¹H NMR (600 MHz, CD₃OD) δ: 8.09 (2H, d, *J* = 8.5 Hz), 7.02 (2H, d, *J* = 8.5 Hz), 6.71 (1H, s), 5.51 (1H, d, *J* = 1.4 Hz), 5.28 (1H, d, *J* = 7.5 Hz), 3.36—4.51 (10H, m), 1.25 (3H, d, *J* = 6.5 Hz); ¹³C NMR (150 MHz, CD₃OD) δ: 177.1 (s), 160.9 (s), 157.0 (s), 152.3 (s), 151.0 (s), 144.4 (s), 133.4 (s), 131.4 (d), 126.9 (s), 121.2 (s), 114.9 (d), 105.2 (s), 101.0 (d), 99.4 (d), 99.2 (d), 77.5 (d), 76.3 (d), 74.4 (d), 72.3 (d), 70.6 (t), 70.4 (d), 70.2 (d), 70.1 (d), 61.0 (t), 18.1 (q).

Rhodosin (**5**).^[3] yellowish powder, C₂₇H₃₀O₁₆, ¹H NMR (600 MHz, CD₃OD) δ: 8.15 (2H, d, *J* = 8.6 Hz), 6.88 (2H, d, *J* = 8.6 Hz), 6.62 (1H, s), 5.54 (1H, d, *J* = 1.9 Hz), 4.67 (1H, d, *J* = 7.1 Hz), 4.18—4.30 (2H, m), 3.67—3.81 (4H, m), 3.35—3.42 (4H, m), 1.28 (3H, d, *J* = 6.2 Hz); ¹³C NMR (150 MHz, CD₃OD) δ: 176.8 (s), 160.3 (s), 153.2 (s), 150.8 (s), 148.6 (s), 145.7 (s), 137.1 (s), 130.8 (d), 128.4 (s), 123.6 (s), 116.2 (d), 106.1 (d), 105.5 (s), 100.3 (d), 99.0 (d), 82.1 (d), 77.6 (d), 77.5 (d), 75.3 (d), 72.2 (d), 71.1 (d), 71.0 (d), 70.6 (d), 62.3 (t), 18.2 (q).

Kaempferol-3-O-β-D-glucopyranoside-(2→1)-D-xylopyranoside (**6**).^[12] yellowish powder, C₂₆H₂₈O₁₅, ¹H NMR (600 MHz, CD₃OD) δ: 8.05 (2H, d, *J* = 8.5 Hz), 6.88 (2H, d, *J* = 8.5 Hz), 6.39 (1H, d, *J* = 1.9 Hz), 6.20 (1H, d, *J* = 1.9 Hz), 5.50 (1H, d, *J* = 5.9 Hz), 4.72 (1H, d, *J* = 7.3 Hz), 4.24—4.29 (2H, m), 3.65—3.76 (2H, m), 3.38—3.41 (2H, m), 3.35—3.37 (3H, m), 3.22—3.29 (2H, m); ¹³C NMR (150 MHz, CD₃OD) δ: 177.1 (s), 165.0 (s), 160.8 (s), 158.4 (s), 156.6 (s), 154.6 (s), 132.6 (s), 130.6 (d), 120.6 (s), 115.1 (d), 104.4 (d), 102.5 (s), 99.6 (d), 97.6 (d), 93.7 (d), 81.5 (d), 76.9 (d), 76.2 (d), 76.1 (d), 73.2 (d), 70.0 (d), 69.4 (d), 65.3 (t), 60.3 (t).

Kaempferol-3-O-β-D-glucopyranosyl-7-O-α-L-rhamnopyranoside (**7**).^[12] white powder, C₂₇H₃₀O₁₅, ¹H NMR (600 MHz, CD₃OD) δ: 8.06 (2H, d, *J* = 8.7 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 6.68 (1H, d, *J* = 2.0 Hz), 6.40 (1H, d, *J* = 2.0 Hz), 5.55 (1H, d, *J* = 1.4 Hz), 5.26 (1H, d, *J* = 7.4 Hz), 3.38—4.49 (10H, m), 1.25 (3H, d, *J* = 6.5 Hz); ¹³C NMR (150 MHz, CD₃OD) δ: 177.6 (s), 161.5 (s), 160.7 (s), 160.1 (s), 156.9 (s), 155.9 (s), 133.6 (s), 131.0 (d), 120.9 (s), 114.3 (d), 105.6 (s), 100.6 (d), 100.2 (d), 99.3 (d), 94.6 (d), 77.5 (d), 76.6 (d), 74.1 (d), 71.6 (d), 70.2 (d), 70.1 (d), 70.0 (d), 69.6 (d), 60.8 (t), 18.1 (q).

Herbacetin-8-O-β-D-glucopyranoside (**8**).^[12] white powder, C₂₁H₂₀O₁₂, ¹H NMR (600 MHz, CD₃OD) δ: 8.16 (2H, d, *J* = 8.6 Hz), 6.89 (2H, d, *J* = 8.6 Hz), 6.60 (1H, s), 5.23 (1H, d, *J* = 7.4 Hz), 3.21—3.69 (6H, m); ¹³C NMR (150 MHz, CD₃OD) δ: 177.4 (s), 160.3 (s), 157.1 (s), 157.0 (s), 156.7 (s), 148.4 (s), 133.3 (s), 131.5 (d), 125.3 (s), 120.6 (s), 115.0 (d), 103.2 (s), 100.7 (d), 99.3 (d), 77.1 (d), 76.6 (d), 74.1 (d), 70.0 (d), 60.7 (t).

Rhodonin (**9**).^[3] greenish powder, C₂₁H₂₀O₁₁, ¹H NMR (600 MHz, CD₃OD) δ: 8.19 (2H, d, *J* = 8.6 Hz), 6.89 (2H, d, *J* = 8.6 Hz), 6.62 (1H, s), 5.51 (1H, d, *J* = 1.7 Hz), 4.13 (1H, s), 3.42—3.84 (3H, m), 1.25 (3H, d, *J* = 6.2 Hz); ¹³C NMR (150

Table 1 Agonistic activities of the isolated compounds on receptor 5-HT_{2A}^a

Compounds	Concentration/mM	Agonistic rate ^b /%	Compounds	Concentration/mM	Agonistic rate ^b /%
1	0.97	9.2	9	1.01	17.3
2	0.95	22.5	10	0.96	7.3
3	1.01	16.7	11	0.98	4.6
4	1.03	18.2	12	1.02	33.5
5	0.97	22.4	13	1.03	42.1
6	1.01	8.0	14	0.96	46.2
7	0.99	18.4	15	0.98	37.6
8	1.03	23.1			

^a The positive control was serotonin hydrochloride (EC₅₀ 8.53 nM). ^b The agonistic rate was percentage versus the positive control (normalized to 100%) and was average of two independent tests.

MHz, CD₃OD) δ : 177.2 (s), 160.5 (s), 153.5 (s), 151.5 (s), 148.7 (s), 145.8 (s), 137.1 (s), 130.9 (d), 128.4 (s), 123.6 (s), 116.2 (d), 106.1 (s), 100.6 (d), 99.0 (d), 73.4 (d), 72.1 (d), 71.5 (d), 71.0 (d), 18.0 (q).

Genistein (**10**):^[13] yellowish powder, C₁₅H₁₀O₅, ¹H NMR (600 MHz, CD₃OD) δ : 8.26 (1H, s), 7.27 (2H, d, *J* = 8.5 Hz), 6.75 (2H, d, *J* = 8.5 Hz), 6.39 (1H, d, *J* = 2.0 Hz), 6.18 (1H, d, *J* = 2.0 Hz); ¹³C NMR (150 MHz, CD₃OD) δ : 180.5 (s), 164.5 (s), 162.3 (s), 157.8 (s), 157.6 (s), 154.2 (d), 130.4 (d), 122.5 (s), 121.4 (s), 115.4 (d), 104.6 (s), 99.2 (d), 93.9 (d).

Genistin (**11**):^[14] yellow powder, C₂₁H₂₀O₁₀, ¹H NMR (600 MHz, DMSO-*d*₆) δ : 8.31 (1H, s), 7.44 (2H, d, *J* = 8.6 Hz), 7.05 (2H, d, *J* = 8.6 Hz), 6.33 (1H, d, *J* = 2.1 Hz), 6.17 (1H, d, *J* = 2.1 Hz), 4.87 (1H, d, *J* = 7.1 Hz), 3.10—3.70 (6H, m); ¹³C NMR (150 MHz, DMSO-*d*₆) δ : 154.7 (d), 122.5 (s), 180.5 (s), 162.3 (s), 99.4 (d), 163.9 (s), 94.2 (d), 157.7 (s), 105.4 (s), 124.3 (s), 130.2 (d), 116.0 (d), 157.3 (s), 100.2 (d), 73.3 (d), 76.7 (d), 69.7 (d), 77.2 (d), 60.7 (t).

Tyrosol (**12**):^[15] white powder, C₈H₁₀O₂, ¹H NMR (600 MHz, CD₃OD) δ : 7.07 (2H, d, *J* = 8.3 Hz), 6.66 (2H, d, *J* = 8.3 Hz), 3.75 (2H, t, *J* = 7.1 Hz), 2.78 (2H, t, *J* = 7.1 Hz); ¹³C NMR (150 MHz, CD₃OD) δ : 156.5 (s), 130.8 (s), 130.6 (d), 116.1 (d), 64.5 (t), 39.2 (t).

Salidroside (**13**):^[16] white powder, C₁₄H₂₀O₇, ¹H NMR (600 MHz, CD₃OD) δ : 7.07 (2H, d, *J* = 8.3 Hz), 6.68 (2H, d, *J* = 8.3 Hz), 4.31 (1H, d, *J* = 7.8 Hz), 4.01—4.04 (1H, m), 2.84—3.05 (3H, m); ¹³C NMR (150 MHz, CD₃OD) δ : 156.9 (s), 130.9 (d), 130.8 (s), 116.2 (d), 104.5 (d), 78.2 (d), 78.0 (d), 75.2 (d), 72.2 (t), 71.7 (d), 62.8 (t), 36.5 (t).

Rosin (**14**):^[12] white powder, C₁₅H₂₀O₆, ¹H NMR (600 MHz, CD₃OD) δ : 7.39—7.41 (1H, m), 7.26—7.27 (2H, m), 7.21—7.24 (2H, m), 6.65 (1H, d, *J* = 16.1 Hz), 6.30—6.34 (1H, m), 4.51 (1H, d, *J* = 7.5 Hz), 4.29—4.36 (2H, m), 3.67—3.87 (2H, m), 3.32—3.38 (4H, m); ¹³C NMR (150 MHz, CD₃OD) δ : 137.3 (s), 132.7 (d), 128.7 (d), 127.6 (d), 126.5 (d), 125.8 (d), 102.5 (d), 77.1 (d), 77.0 (d), 74.2 (d), 70.8 (d), 69.9 (t), 61.6 (t).

Rosavin (**15**):^[12] white powder, C₂₀H₂₈O₁₀, ¹H NMR (600 MHz, CD₃OD) δ : 7.40—7.44 (2H, m), 7.28—7.29 (2H, m), 7.19—7.23 (1H, m), 6.68 (1H, *J* = 16.3 Hz), 6.30—6.35 (1H, m), 4.50—4.51 (1H, m), 4.29—4.32 (1H, m), 4.37 (1H, d, *J* = 7.6 Hz), 4.34 (1H, d, *J* = 7.2 Hz), 4.07—4.11 (1H, m), 3.74—3.85 (3H, m), 3.24—3.57 (6H, m); ¹³C NMR (150 MHz, CD₃OD) δ : 138.5 (s), 133.8 (d), 129.7 (d), 128.7 (d), 127.6 (d), 126.8 (d), 103.5 (d), 105.2 (d), 78.1 (d), 77.0 (d), 75.1 (d), 74.3 (d), 72.5 (d), 71.8 (d), 70.9 (t), 69.6 (d), 69.5 (t), 66.8 (t).

Pharmacological studies demonstrated that the selective agonists of serotonin (5-HT) receptor 5-HT_{2A} were closely involved in the therapy of hypertension, hyperlipidemia and obesity.^[5,6] Consequently, these isolates from the title plant were further assayed for their agitating activities on 5-HT_{2A} receptor on HEK293 cell lines *in vitro*.

As shown in Table 1, the bioassay results revealed that all the test compounds exhibit varying agitating activities against the 5-HT_{2A} receptor. Among them, rosin (**14**) exhibits the

strongest effect with an agonistic rate of 46.2% at the concentration of 0.96 mM, following by salidroside (**13**), rosavin (**15**) and tyrosol (**12**) with agonistic rates of 42.1%, 37.6% and 33.5% at about 1.00 mM, respectively.

In conclusion, 11 flavonoids, 2 phenylethanoids and 2 phenylpropanoids were isolated from the roots of *R. rosea* L. Among them, flavones **1** and **2** were isolated from the *Rhodiola* genus for the first time. The bioassay results revealed that rosin (**14**), salidroside (**13**), rosavin (**15**) and tyrosol (**12**) are probably the main lipid-lowering components of *R. rosea* L., which may provide additional information for the further development of this medicine-food resource plant.

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Supporting Information

The bioassay results of extracts and fractions on receptor 5-HT_{2A} are available in Supporting Information.

Conflict of Interest

The authors declare no conflict of interest.

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