A new methylene bisflavan-3-ol from the branches and leaves of Potentilla fruticosa

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ABSTRACT

Dasiphora fruticosa L. (Rosaceae), also known as Potentilla fruticosa L. (syn.), is a hardy deciduous shrub widely distributed in the north temperate regions of the world. Three methylene bisflavan-3-ols (1-3), together with a procyanidin dimer, (-)-afzelein-(4α-8)-(-)-afzelein (4) were isolated for the first time from the branches and leaves of the titled plant, in addition to 11 known compounds (5-15). Their structures were elucidated by means of extensive spectroscopic analysis and by comparison with data reported in the literatures. Methylene 6,8-bis(7-O-glucosyl) catechin (1) was determined to be a new dimeric flavan-3-ol glycoside through a methylene linkage between C-8 and C-8 of two units. At a concentration of 128 μg/mL, the known compounds 9 – 13 exhibited antibacterial activities on Escherichia coli, Staphylococcus aureus subsp. aureus, Salmonella enterica subsp. enterica, and Pseudomonas aeruginosa. Compound 12 also showed certain glucose uptake stimulating activity.
1. Introduction

The genus Potentilla L. (Rosaceae), comprising about 500 species is widely distributed in the temperate regions of the northern hemisphere of Europe, Asia and America, as well as Chile, New Zealand and Australia, with about 90 species growing in China (The flora of China’s editorial board 1985; Sun et al. 2010). Many Potentilla species have been used commonly as traditional medicine for the treatment of inflammations, wounds, cancer, diarrhoea, diabetes, and infections caused by bacteria, fungi and virus. More than 100 compounds including flavonoids, terpenoids, and tannins were isolated from some Potentilla species (Tomczyk & Latté 2009).

Dasiphora fruticosa (L.) Rydb, also known as Potentilla fruticosa L. (syn.), Dasiphora riparia Raf. (syn.), and Pentaphylloides fruticosa (L.) O. Schwarz (syn.), is a hardy deciduous shrub widely distributed in the north temperate regions of the world, often growing in the grassland, meadow, alpine bushes and edge of the forest with high altitudes of 1000 - 4200 m (The flora of China’s editorial board 1985). Because of the hardiness and low maintenance, it is a popular ornamental plant with dozens of small, flat, and round flowers on each bush. The whole plants of D. fruticosa displayed various pharmacological activities, particularly the antimicrobial and anti-viral activities, as well as the repairment potential for immune system (Tomczyk et al. 2008; Tomczyk & Latté 2009). The branches and leaves with potential effects to reduce cholesterol and sugar levels in blood have also been used as food additives (Havsteen 1983). The leaf extract of D. fruticosa was reported to contain higher amounts of hyperoside, ellagic acid and (+)-catechin, which displayed significant antioxidant activity in vitro and protective effects on Escherichia coli under peroxide stress (Luo et al. 2016). Moreover, the combination of D. fruticosa leaf extracts (PFE) with green tea polyphenols (GTP) at a ratio of 3:1 exhibited stronger synergistic effect, due to the promotion of CAT and SOD genes expression and enhancing the activities of CAT and SOD enzyme (Liu et al. 2018). In order to explore the bioactive components of the titled plant, the branches and leaves of D. fruticosa were studied chemically, which led to the isolation and identification of 15 compounds. Their structures were determined on the basis of detailed spectroscopic analyses and compared with literature values. Considering the reported bioactivity for the whole plants and the leaves, all the isolates were tested for their anti-bacterial and the glucose uptake stimulating activities.

2. Results and discussion

The EtOAc and H2O fractions of the branches and leaves of D. fruticosa were applied to repeated column chromatography (CC) over Sephadex LH-20, MCI-gel CHP20P, Rp-18, Toyopearl HW-40F, and silica gel to afford three methylene bisflavan-3-ols (1-3), one procyanidin dimer (4), and other 11 known phenolic compounds (5-15). The known ones 2-15 were identified as bis-6,8-catechinylmethane (2) (Boyer & Ducrot 2005), bis-8,8-catechinylmethane (3) (She et al. 2009), and afzelechin-(4×−8)-afzelchin (4) (Kashiwada et al. 1990), quercetin 7-O-β-D-glucuronide (5) (Shaker et al. 2015), quercetin (6) (Zou et al. 2015), 1,6-di- (7), 1,2,3,6-tetra- (8) 3,4,6-tri- (9) O-galloyl-β-D-glucose (Olennikov et al. 2015), caffeic acid (10) (Tu et al. 1999), naringeninic acid (11) (Salum et al. 2010), 5-hydroxysalicylic acid (12) (Santoso et al. 2016), methyl gallate...
(Ouyang et al. 2007), protocatechuic acid (Thai et al. 2016), and gallic acid (Okuda et al. 1982), by comparison of their spectroscopic data with literature values. All of them were isolated from the P. fruticose for the first time.

Compound 1 was obtained as a yellowish amorphous powder. Its molecular formula was deduced to be C_{43}H_{48}O_{22}, on the basis of the positive ion HRESIMS (m/z 939.2526 [M + Na]+). The IR spectrum showed the existence of hydroxy group (3421 cm⁻¹) and benzene rings (1617 and 1441 cm⁻¹). The ¹H NMR spectrum displayed characteristic signals for two flavan-3-ol C-rings (δ_H 4.76/4.44 (H-2), 4.07/3.88 (H-3), 2.85/2.80 (H-4a), 2.60/2.41 (H-4b)), two 1,3,4-trisubstituted benzene rings [unit A: δ_H 6.83 (1H, d, J = 1.9 Hz, H-2'), 6.76 (1H, d, J = 8.0 Hz, H-5'), 6.61 (1H, dd, J = 8.0, 1.9 Hz, H-6'); unit B: δ_H 6.75 (1H, d, J = 2.0 Hz, H-2'), 6.72 (1H, d, J = 8.0 Hz, H-5'), 6.72 (1H, dd, J = 8.0, 2.0 Hz, H-6')], and two anomic protons [δ_H 4.78 (d, J = 7.9 Hz), 4.77 (d, J = 8.0 Hz)]. In the ¹³C NMR (DEPT) spectra of 1, beside a methylene at δ_C 17.7, the other 42 carbon signals appeared all as a pair, arising from two sets of glucosyls [δ_C 102.7, 102.3 (C-1"), 74.6, 74.8 (C-2"), 78.0, 78.10 (C-3"), 71.2, 71.3 (C-4"), 78.3, 78.2 (C-5"), 63.2, 62.5 (C-6")], and two catechinyls [δ_C 83.2/83.6 (C-2), 68.9/68.2 (C-3), 29.6/28.3 (C-4)]. According to the coupling constants of J₃,₄ in the ¹H NMR spectrum and the ¹³C NMR data of C-2/C-3 (J₃,₄a = 4.1 Hz/J₃,₄b = 4.1 Hz, δ_C 79.9 (C-2)/67.5 (C-3) for (-)-epicatechin, and J₃,₄a = 5.5 Hz/J₃,₄b = 8.4 Hz, δ_C 82.9 (C-2)/δ_C 68.9 (C-3) for (+)-catechin) (Seto et al. 1997), the two flavan-3-ol units in 1 (J₃,₄a = 7.7/8.1 Hz, J₃,₄b = 5.3/5.6 Hz, δ_C 83.2/83.6, δ_C 68.9/68.2) were concluded both as catechin. However, instead of four aromatic A-ring methines (2 × C_2/C_6, 2 × C_8) for two catechin units, the NMR data of 1 displayed only two aromatic methines (δ_C 96.2 and 95.8) for two catechinyl A-rings and other two additional quaternary aromatic carbons at δ_C 110.6 and 108.9 as well as an additional benzylic methylene [δ_H 4.03, 3.85 (each 1H, d, J = 15.0 Hz); δ_C 17.4 (CH₂)]. These NMR data indicated that the two catechin units in 1 were connected between their C-6 or C-8 positions through a methylene bridge.

The connective position of the two catechin units was further confirmed by 2D NMR experiments. In the HMBC spectrum of 1 (Figure S1), correlations from δ_H 4.76 (H-2) to δ_C 153.7 (C-9), 131.4 (C-1'), 115.4 (C-2'), 120.2 (C-6') and 28.4 (C-4), and from δ_H 2.85 and 2.60 (H-4) to δ_C 68.2 (C-3), 83.6 (C-2), 103.2 (C-10), 153.7 (C-9) and 156.3 (C-5) assigned those signals to one of the catechinyl unit (upper one), while, signals from the second catechinyl unit (lower one) were determined by the HMBC correlations from δ_H 2.80, 2.41 (H-4) to δ_C 68.9 (C-3), δ_C 83.2 (C-2), δ_C 104.4 (C-10), δ_C 154.7 (C-9) and δ_C 155.2 (C-5), and from δ_H 4.44 (H-2) to δ_C 154.7 (C-9), δ_C 132.2 (C-1'), δ_C 115.7 (C-2'), δ_C 120.5 (C-6') and δ_C 29.6 (C-4). Moreover, the benzylic methylene protons at δ_H 4.03 and 3.85 displayed HMBC correlations with the upper C-5 (δ_C 156.3) and C-7 (δ_C 156.3), and the lower C-9 (δ_C 154.7) and C-7 (δ_C 155.7), indicating that the two catechin units in 1 were linked between the upper C-6 and the lower C-8 positions through a methylene bridge. The two glucosyl units were confirmed to be both at the catechinyl C-7, according to the ROESY and HMBC correlations of the glucosyl H-1" (δ_H 4.78) with the upper H-8 (δ_H 6.29) and C-7 (δ_C 156.3), and glucosyl H-1" (δ_H 4.77) with the lower H-6 (δ_H 6.18) and C-7 (δ_C 155.7). One the basis of the above evidence, compound 1 was determined to be methylene 6,8-bis(7-O-glucosyl)catechin.
Figure 1. Compounds 1–15 isolated from Potentilla fruticosa.
Compounds 1-15 were evaluated for their anti-bacterial activities against *Escherichia coli* (BEC), *Staphylococcus aureus* subsp. *aureus* (BSA), *Salmonella enterica* subsp. *enterica* (BSE), and *Pseudomonas aeruginosa* (BPA), with ceftazidime and penicillin G sodium as positive controls. The results were shown on Table S2. At a concentration of 128 μg/mL, compounds 9-13 showed anti-bacterial activities on BEC (9, 12 and 13), BSA (10 and 11), BSE (11 and 13), and BPA (9), with the inhibitory ratios of 48.9%, 31.3%, 50.9%, 52.1%, 55.2%, 39.5%, 37.2%, and 36.6%, respectively. Moreover, among all the isolates, only 12 showed weak glucose uptake stimulating activity at a concentration of 25 μM (Table S3).

3. Experimental

3.1. General

Shown in supporting information.

3.2. Plant Material

The branches and leaves of *Dasiphora fruticosa* were collected in Qinghai Province, China, in July 10-12, 2015 and identified by Professor Zhen-Ning Chen of Qinghai Normal University, China. A voucher specimen (QNU-SLC-2015009) has been deposited in School of Life Science, Qinghai Normal University.

3.3. Extraction and isolation

The air-dried branches and leaves (35 kg) of *D. fruticosa* was extracted three times with 95% methanol by reflux. After removal of organic solvent, the concentrated extract (4.2 kg) was suspended into water and extracted successively with petroleum ether and EtOAc. A portion (300 g) of EtOAc fraction (1.05 kg) was applied to column chromatography (CC) over Sephadex LH-20, eluting with MeOH-H2O (0:1-1:0), to afford eight fractions (Fr. E1-Fr. E8). Fr. E4 (22.0 g) was subjected to repeated CC over Sephadex LH-20 (MeOH-H2O, 0:1–1:0), MCI-gel CHP20P (MeOH-H2O, 0:1–1:0) and Rp-18 (MeOH - H2O, 2:8 – 10:0) to afford compounds 1 (4.0 mg), 5 (65 mg) and 6 (12 mg). Similarly, Fr. E5 (10 g) was chromatographed over Sephadex LH-20 (MeOH - H2O, 0:1–1:0), MCI-gel CHP20P (MeOH-H2O, 0:1–1:0), Rp-18 (MeOH-H2O, 2:8–7:3), Toyopearl HW-40F (MeOH-H2O, 1:9–8:2) to give compounds 3 (18 mg), 4 (9.0 mg), 9 (8.0 mg), 13 (21 mg) and 14 (4.0 mg). Fr. E6 (20 g) was subjected to CC over Sephadex LH-20 (MeOH-H2O, 0:1–1:0), MCI-gel CHP20P (MeOH-H2O, 0:1–1:0), Rp-18 (MeOH-H2O, 1:9–6:4) and silica gel (CHCl3-MeOH-H2O, 9:1:0.1–6:4:1) to yield compounds 10 (4.3 mg), 11 (10 mg), 12 (5.0 mg), and 15 (11 mg).

A portion (300 g) of H2O fraction (1.28 kg) was applied to Sephadex LH-20 CC, eluting with methanol/water (0:1-1:0) to afford five fractions (Fr. W1-Fr. W5). Fr. W3 (8 g) was subjected to repeated CC over Sephadex LH-20 (MeOH-H2O, 0:1–1:0), MCI-gel CHP20P (MeOH-H2O, 0:1–1:0), and Toyopearl (MeOH-H2O, 2:8–5:5) to yield compounds 2 (7.4 mg), 7 (8.0 mg) and 8 (14 mg).
3.3.1. Compound 1

Yellowish amorphous powder; [α]D$^25$ – 118.2 (c 0.1, methanol). HRESIMS (m/z 939.2526 [M + Na]$^+$, calcd. for C₄₃H₄₈O₂₂Na, 939.2529). IR (KBr): $\nu_{max}$ (methanol) (log ε): 276 (0.16), 222 (0.39) nm. UV $\lambda_{max}$: 4.03, 3.85 (each 1H, d, $J = 15.0$ Hz, CH₂), upper unit: 4.76 (1H, d, $J = 7.7$ Hz, H-2), 4.07 (1H, m, H-3), 2.85 (1H, dd, $J = 16.5$, 5.3 Hz, H-4a), 2.60 (1H, dd, $J = 16.5$, 7.7 Hz, H-4b), 6.29 (1H, s, H-8), 6.83 (1H, d, $J = 1.9$ Hz, H-2′), 6.76 (1H, d, $J = 8.0$ Hz, H-5′), 6.61 (1H, dd, $J = 8.0$, 1.9 Hz, H-6′), 4.78 (1H, d, $J = 7.9$ Hz, H-1″), 3.35-3.95 (6H, m, H-2″-6″); lower unit: 4.44 (1H, d, $J = 8.1$ Hz, H-2), 3.88 (1H, m, H-3), 2.80 (1H, dd, $J = 16.4$, 5.6 Hz, H-4a), 2.60 (1H, d, $J = 16.4$, 8.1 Hz, H-4b), 6.18 (1H, s, H-6), 6.75 (1H, d, $J = 2.0$ Hz, H-2′), 6.72 (1H, d, $J = 8.0$ Hz, H-5′), 6.72 (1H, dd, $J = 8.0$, 2.0 Hz, H-6′), 4.77 (1H, d, $J = 8.0$ Hz, H-1″), 3.35-3.95 (6H, m, H-2″-6″). 13C NMR (150 MHz, CD₃OD): δC 17.4 (CH₂), upper unit: 83.6 (C-2), 68.2 (C-3), 28.4 (C-4), 156.3 (C-5), 108.9 (C-6), 156.3 (C-7), 96.2 (C-8), 153.7 (C-9), 103.2 (C-10), 131.4 (C-1″), 115.4 (C-2″), 146.5 (C-3″), 145.3 (C-4″), 116.2 (C-5″), 120.2 (C-6″), 102.3 (C-1″′), 74.6 (C-2″′), 78.3 (C-3″′), 71.2 (C-4″′), 78.1 (C-5″′), 62.3 (C-6″′). lower unit: 83.2 (C-2), 68.9 (C-3), 29.6 (C-4), 155.2 (C-5), 95.8 (C-6), 155.7 (C-7), 110.6 (C-8), 154.7 (C-9), 104.4 (C-10), 132.2 (C-1″), 115.7 (C-2″), 146.5 (C-3″), 146.4 (C-4″), 116.3 (C-5″), 120.5 (C-6″), 102.6 (C-1″″), 74.8 (C-2″″), 78.2 (C-3″″), 71.3 (C-4″″), 78.1 (C-5″″), 62.5 (C-6″″).

3.4. Anti-bacterial assay

The assay was performed according to the Performance standards (Clinical Lab Standards Institute 2009). Briefly, a mixture of tested sample (100 μL) and bacteria (1 × 10⁶ CFU/mL, 100 μL) was added to the 96-well plates. After culturing at 37 °C for 24 hrs, the OD value of each well was recorded by ELISA under 625 nm. Blank control (culture medium), bacterial control, and positive control (ceftazidime and penicillin G sodium) were set up at the same time. The inhibition values (%) were obtained according to the following equation.

\[
\text{Inhibition} \% = \left(1 - \frac{\text{OD}_{\text{sample}}}{\text{OD}_{\text{bacteria}}} \right) \times 100\%
\]

3.5. Glucose uptake assay

The assay for glucose uptake was conducted with minor modifications (Zhou et al. 2007; Hu et al. 2015), and 3T3-L1 fibroblasts (ATCC, USA) were cultured and differentiated into adipocytes as reported (Xiong et al. 2010). Differentiated adipocytes were plated into 96-well plates and pre-incubated with FBS-DMEM containing BSA (0.2%) for 12 hours, and then further incubated for 24 hrs with either 25 μM compounds (1–15) or insulin (0.1 μM) or berberine (10 μM) as positive controls, or DMSO as negative control. The medium (10 μL) was collected to determine its glucose concentrations by the glucose oxidase method using a Glucose Kit. The amount of glucose uptake was calculated by the glucose concentrations of blank wells subtracting the remaining glucose in the cell-plated wells. At the same time, the remaining medium was added with 20 μL of 3-(4,5-dimethylthiazol-2-yl)-5(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS). The absorption at 492 nm was measured after incubation at 37 °C for 2 hrs to determine the toxicity of the tested sample to adipocytes.
4. Conclusion

Fifteen compounds 1-15 including three methylene bisflavan-3-ols (1-3) and one procyanidin dimer (4) were isolated from the branches and leaves of Dasiphora fruticosa. The new compound 1 was determined to be methylene 6,8-bis(7-O-glucosyl)catechin. All the isolates 1-15 were reported from the titled plant for the first time. The known ones 9-13 displayed obvious antibacterial activities on E. coli, S. aureus subsp. aureus, S. enterica subsp. enterica, and P. aeruginosa. Moreover, compound 12 showed weak glucose uptake stimulating activity, which may be related to the folk uses of this plant.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix A: Supplementary data

General of experiment, the anti-bacterial and glucose uptake stimulating activities of 1–15, the 1D, 2D NMR, HRESIMS, IR, UV, and OR spectra of compound 1 are available.