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MODIFIED DEHYDROELLAGITANNINS FROM *DAVIDIA INVOLUCRATA* LEAVES

Akari Esumi, Hiroe Aoyama, Yuuki Shimozu, Shoko Taniguchi, and Tsutomu Hatano*

Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Tsushima-naka, Kita-ku, Okayama 700-8530, Japan. E-mail: hatano-t@cc.okayama-u.ac.jp

Abstract – *Davidia involucrata* (Nyssaceae) is a naturally rare plant found in southern China. We isolated two previously undescribed ellagitannins, davicratinic acid B (**5**) and C (**6**), in addition to four known compounds, davicratinic acid A (**1**), helioscopinin B (**2**), granatin A (**3**), and pedunculagin (**4**). Spectral analyses revealed that compounds **5** and **6** are modified dehydroellagitannins with isomeric structures.

INTRODUCTION

Davidia involucrata Baillon is a naturally rare tree in southern China. Although this species was previously considered a member of the Davidiaceae family according to the Engler system[1] or of the Cornaceae according to the Cronquist system,[2] it is currently classified in the Nyssaceae family according to the modern APG system.[3] The presence of ellagitannins, including the uniquely structured davidiin, in this plant species was reported by Haslam and co-workers.[4] Recently, our group reported the structure of the ellagitannin davicratinic acid A (**1**) from this species.[5] Our continuing investigation of the chemical constituents of *D. involucrata* revealed several unidentified ellagitannins in the leaves. The structures of two such compounds are elucidated herein.

RESULTS AND DISCUSSION

Dried leaves of *D. involucrata* were homogenized in 70% aqueous acetone, and the concentrated filtrate from the homogenate was extracted with chloroform, ethyl acetate, and *n*-butanol, successively. The remaining aqueous solution after extraction was separated chromatographically using Diaion HP-20, Toyopearl HW-40C and HW-40F, MCI-gel CHP-20P, YMC-gel ODS-A, and Sephadex LH-20 columns, yielding fractions containing ellagitannins. Analogous treatment of the *n*-butanol extract also provided an

ellagitannin-rich fraction. These fractions were purified further by preparative HPLC respectively, yielding six ellagitannins. Four of these were identified as davicratinic acid A (**1**),[5] helioscopinin B (**2**),[6] granatin A (**3**),[5] and pedunculagin (**4**)[5] (Figure 1). Note that granatin A, which bears a dehydrohexahydroxydiphenoyl (DHHDP) group, is a representative dehydroellagitannin.[7] The two remaining compounds have not been described previously. Their structures, which identify them as modified dehydroellagitannins, are described below.

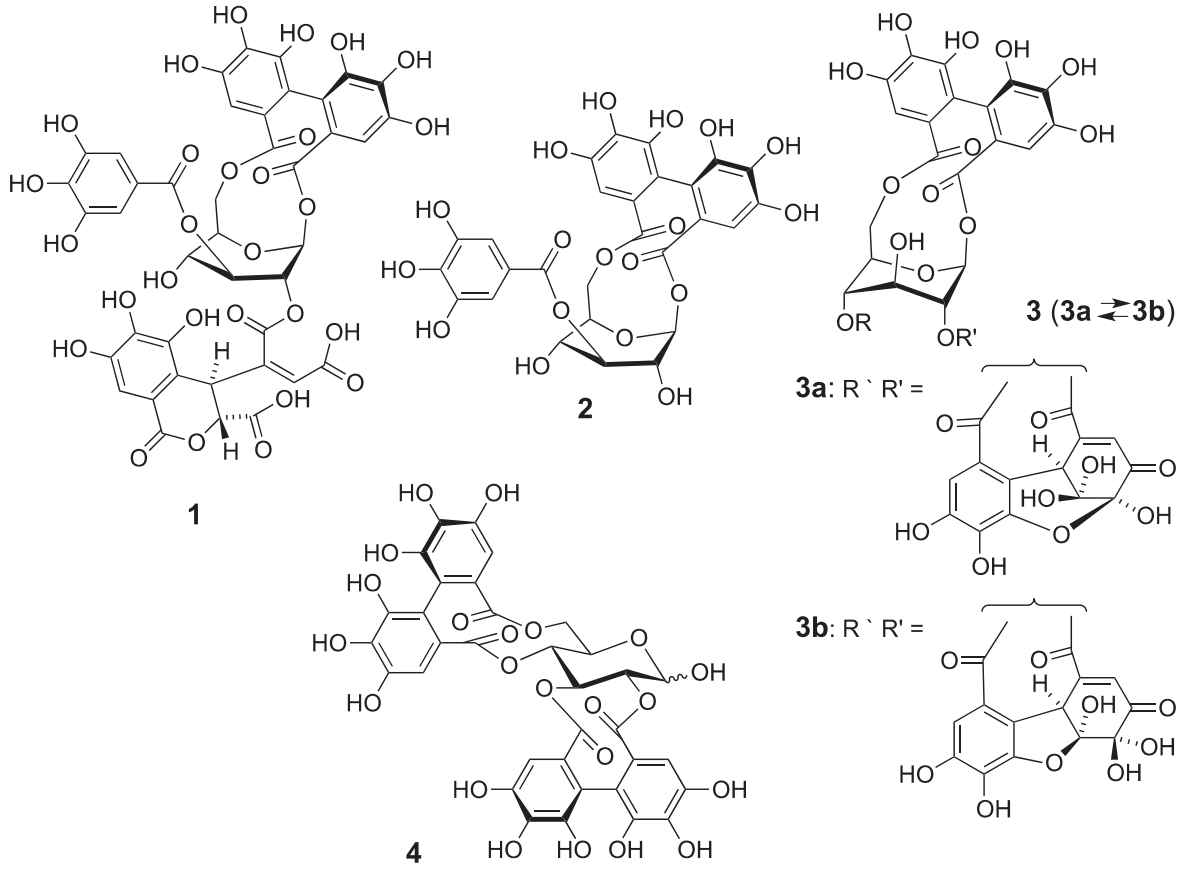

Figure 1. Structures of known ellagitannins isolated from *Davidia involucrata* leaves

Compound **5** was obtained as a pale-yellow amorphous powder. The high-resolution (HR) electrospray-ionization mass spectrometry (ESI-MS) indicated an $[M+NH_4]^+$ ion peak in the spectrum corresponding to its molecular formula $C_{34}H_{24}O_{23}$. The ^{1}H NMR spectrum of **5** in acetone-d_6 containing D_2O shows two singlets corresponding to a hexahydroxydiphenoyl (HHDP) group [δ 6.83 (H-3) and 6.80 (H-3')] and seven proton signals corresponding to a $^1C_4$ glucopyranose core [δ 6.03 (1H, br s, H-1), 5.00 (1H, br m, H-2) , 4.40 (1H, br m, H-3), 4.71 (1H, br m, H-4), 4.72 (1H, dd, *J*=5.4, 12.6 Hz, H-5), 5.00 (1H, dd, *J*=11.4, 12.6 Hz, H-6a), and 4.07 (1H, dd, *J*=5.4, 11.4 Hz, H-6b)]. The chemical shift of glucose (Glc) H-3 indicated that the hydroxyl group of Glc C-3 is unacylated. In addition to these signals, the

spectrum also shows signals of an additional aromatic proton [δ 6.97 (1H, s) (H-3)], a vinylic proton [δ 6.42 (1H, s) (H-5')], and two methine protons [δ 5.23 (d, *J*=6.0 Hz) (H-3') and 5.51 (d, *J*=6.0 Hz) (H-2')] that are mutually coupled to each other. These spectral features suggested a structure related to that of granatin A (**3**), except for the following features: 1) Granatin A (**3**) exists as an equilibrated mixture with regard to the DHHDP group, in which the ketonic carbons can adopt a six-membered hemiketal (**3a**) or five-membered hemiketal structure (**3b**); while such equilibration was not observed for compound **5**. 2) The signal corresponding to H-2' in **5** was absent in the spectrum of granatin A (**3**).

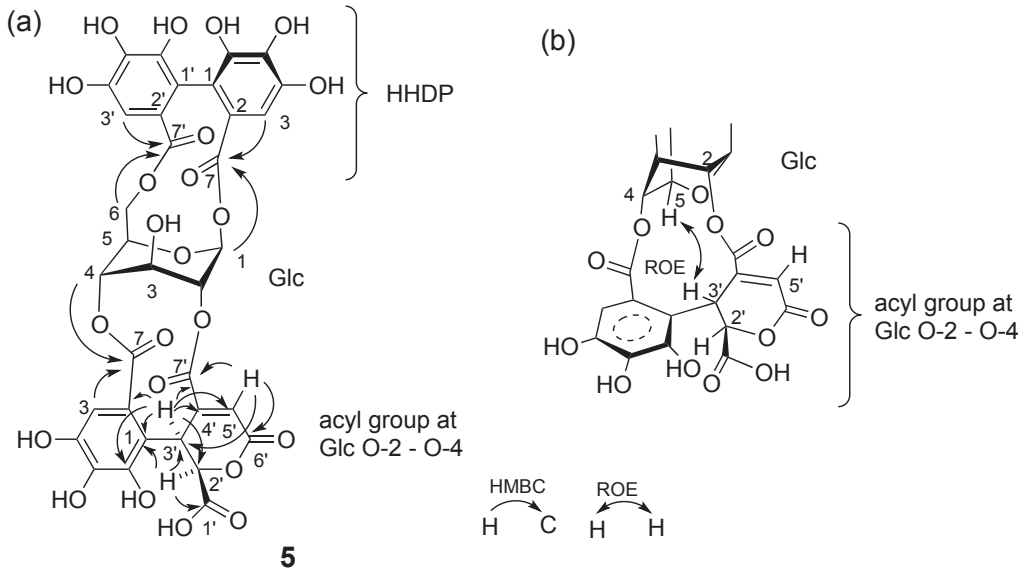

Figure 2. (a) Key HMBC correlations for compound **5**, indicating the locations of the acyl groups on the glucose (Glc) core. (b) Stereochemical relationships of protons H-2', H-3', and H-5' of the acyl group at Glc O-2 and O-4, and the rotating-frame Overhauser effect (ROE) correlation of H-3' and Glc H-5 in the structure of **5**

The presence of an HHDP group [δ 117.2 (C-1), 115.9 (C-1'), 124.9, 125.0 (C-2, C-2'),[8] 109.4 (C-3), 108.5 (C-3'), 144.6 (C-4), 145.0 (C-4'), 136.9 (C-5), 136.4 (C-5'), 144.5 (C-6), 144.6 (C-6'), 166.4 (C-7), and 168.7 (C-7')] and a Glc core [δ 89.7 (C-1), 70.3 (C-2), 62.7 (C-3), 70.7 (C-4), 70.7 (C-5), and 63.6 (C-6)] in **5** was also indicated in its ^{13}C NMR spectrum. The upfield shift of Glc C-3 substantiated that the hydroxyl group at Glc C-3 is unacylated. The location of the HHDP group on the Glc core was confirmed by the following sets of "HHDP proton – HHDP ester carbon – Glc proton" correlations in the HMBC spectrum: (HHDP H-3 – HHDP C-7 – Glc H-1) and (HHDP H-3' – HHDP-C-7' – Glc H-6a) [See Figure 2(a)]. The remaining carbon signals were ascribed to the carbon atoms of the acyl group at O-2 – O-4 on the Glc core: trihydroxyphenoyl residue carbons [δ 113.0 (C-1), 125.4 (C-2),[8] 112.4 (C-3), 145.2 (C-4), 138.0 (C-5), 146.2 (C-6), and 167.5 (C-7)] and dihydropyranone moiety carbons [δ 168.6 (C-1'), 79.1 (C-2'), 37.5 (C-3'), 148.8 (C-4'), 123.7 (C-5'), 163.3 (C-6'), 165.1 (C-7')]. The HMBC spectrum shows

the following correlations, and substantiates the connectivity, between protons on the acyl group and neighboring carbon atoms: H-3' with C-2', C-4', C-5', C-7', C-1, C-2, and C-6; H-2' with C-1', C-3', and C-1; and H-5' with C-3', C-6', and C-7' [Figure 2(a)]. The lactone formation of OH at C-2' with the carboxyl of C-6' was shown by the upfield shift of C-6' (δ 163.3) relative to the other ester carbonyl or carboxyl carbon signals and the molecular formula $C_{34}H_{24}O_{23}$ for this compound. The HMBC spectrum of **5** also shows the H-3 – C-7 – Glc H-4 correlations concerning the acyl group, thereby substantiating the location of the trihydroxyphenoyl moiety of the acyl group with the hydroxyl group at Glc C-4 [Figure 2(a)].

The CD spectrum of **5** contained a broad positive peak at approximately 250–220 nm ($[\theta]_{242}$ $+9.5 \times 10^4$, $[\theta]_{226}$ $+1.6 \times 10^5$) and a negative peak at around 200 nm ($[\theta]_{200}$ -1.5×10^5; the shortest wavelength measured). These data are similar to the CD spectrum of granatin A (**3**), corresponding to an S_a-configuration[9] of the HHDP group ($[\theta]_{238}$ $+1.0 \times 10^5$) and an *S*-configuration[10] at the methine carbon of the acyl (DHHDP) group (α-orientation of the methine proton) at glucose O-2 and O-4 ($[\theta]_{222}$ $+1.4 \times 10^4$, $[\theta]_{200}$ -1.1×10^5) in **3**. An S_a-configuration of the HHDP group and an *S*-configuration at C-3' of the acyl group at Glc O-2 and O-4 were thus assigned to compound **5**. The α-orientation of bond C-3' – H-3' was also substantiated by an ROE correlation between H-3' and Glc H-5 [See Figure 2(b)], similarly observed with geraniinic acids B and C,[11] in which methine (H-3') – Glc proton (H-1) NOE correlations were shown. The configuration at C-2' in the acyl group at Glc O-2 and O-4 in **5** was assigned based on the following arguments. The ^{1}H NMR spectrum of granatin A (**3**) shows the vinyl–methine coupling among the DHHDP protons in the five-membered structure (**3b**), whereas such interactions were not observed in the six-membered form (**3a**). As with compound **3a**, allylic coupling between the vinyl proton (H-5') and methine proton H-3' was not observed in the spectrum of **5**. Since the absence of allylic coupling in the six-membered form of dehydroellagitannins is attributable to a co-planar relationship between the vinyl proton (C-5' – H-5' bond) and methine proton (C-3' – H-3' bond),[12] the observations for **5** indicated a *quasi*-equatorial α-oriented C-3' – H-3' bond. Considering the Karplus relationship, the dihedral angle formed by bonds C-2' – H-2' and C-3' – H-3' in the acyl group conformation shown in Figure 2(b) is expected to be between 10° and 30° based on the large coupling constant (6 Hz) between H-2' and H-3'. An α-orientation of the C-2' – H-2' bond (corresponding to an *R*-configuration at C-2'), forming a *cis* relationship between these protons, was thus assigned to **5**. The relationship between the C-2' – H-2' and C-3' – H-3' bonds is in accord with that between the corresponding protons in geraniinic acid C,[11] in which the coupling constant between H-2' and H-3' was reported to be 6 Hz. Further structural correlations between compound **5** and granatin A (**3**) were evidenced by the production of **5** after

treatment of **3** with a mixture of Fe^{2+} and ascorbate, which are often used to initiate lipid peroxidation.[13] This reaction mixture was purified to give product **5**, the identity of which was revealed by comparisons of HPLC retention times and HR-ESI-MS spectra. The structure of **5** which includes the phenylpyranone residue shown in Figure 2, was thus elucidated, and this compound was named davicratinic acid B.

Compound **6** was isolated as a pale-yellow amorphous powder. The HR-ESI-MS spectrum of **6** contains an $[M+Na]^+$ ion peak corresponding to the molecular formula $C_{34}H_{24}O_{23}$, isomeric to compound **5**. The ^1H NMR spectrum of **6** shows signals corresponding to an HHDP group [δ 6.84 (H-3) and 6.75 (H-3')] and a $^1C_4$ glucopyranose core [δ 5.90 (1H, br s, H-1), 4.96 (1H, br m, H-2), 4.44 (1H, br m, H-3), 4.75 (1H, br m, H-4), 4.65 (1H, dd, *J*=5.4, 12.6 Hz, H-5), 5.04 (1H, dd, *J*=11.4, 12.6 Hz, H-6a), and 4.02 (1H, dd, *J*=5.4, 11.4 Hz, H-6b)]. The upfield shift of Glc H-3 in the ^1H NMR spectra indicated the presence of an unacylated hydroxyl group at Glc C-3. The ^{13}C NMR spectrum substantiated the presence of the HHDP group [δ 117.1 (C-1), 115.7 (C-1'), 124.9 (C-2), 125.5 (C-2'), 109.7 (C-3), 108.0 (C-3'), 144.6 (C-4), 145.0 (C-4'), 137.1 (C-5), 136.2 (C-5'), 144.7, 144.6 (C-6, C-6'),[8] 166.7 (C-7), and 168.9 (C-7')] and the $^1C_4$ glucopyranose core [δ 90.0 (C-1), 70.2 (C-2), 62.3 (C-3), 70.6 (C-4), 70.9 (C-5), and 63.9 (C-6)]. The chemical shifts of the Glc carbon signals, which were comparable to those of the corresponding carbons of compound **5** as shown above, also satisfied the presence of the unacylated hydroxyl group at Glc C-3. The remaining ^1H and ^{13}C signals were attributed to an acyl group with a phenylpyranone structure, corresponding to that on Glc O-2 – O-4 in **5**: [δ 7.05 (1H, s, H-3), 5.01 (1H, d, *J*=0.6 Hz, H-2'), 5.35 (1H, m, H-3'), and 6.36 (1H, d, *J*=1.2 Hz, H-5') for ^1H; δ 116.3 (C-1), 123.1 (C-2), 112.1 (C-3), 145.3 (C-4), 138.3 (C-5), 144.3 (C-6),[8] and 167.2 (C-7) (trihydroxyphenoyl moiety); δ 171.4 (C-1'), 80.3 (C-2'), 37.6 (C-3'), 148.5 (C-4'), 123.3 (C-5'), 162.4 (C-6'), and 164.9 (C-7') (dihydropyranone moiety)]. The HMBC spectrum of **6** indicated the location of the acyl groups on the glucopyranose core. Correlations of HHDP H-3 – HHDP C-7 – Glc H-1 and HHDP H-3' – HHDP C-7' – Glc H-6a corresponded to the esterification of the HHDP group with Glc O-1 and O-6, whereas the trihydroxyphenoyl H-3 – trihydroxyphenoyl C-7 – Glc H-4 correlations were indicative of the location of the trihydroxyphenoyl group on Glc O-4 [See Figure 3(a)]. The dihydropyranone moiety of the phenylpyranone residue was therefore assigned on the remaining Glc O-2. The connectivity in the phenylpyranone residue, including lactone formation between the hydroxyl group at C-2' and carboxyl C-6', also corresponded to the HMBC correlations shown in Figure 3(a).

The CD spectrum of **6** contains a broad positive peak at approximately 250–220 nm ($[\theta]_{237}$ $+9.8 \times 10^4$, $[\theta]_{228}$ $+1.2 \times 10^5$) and a negative peak at approximately 200 nm ($[\theta]_{200}$ -1.2×10^5; the shortest

wavelength measured). This spectrum was similar to that of **5**, indicating an S_a-configuration of the HHDP group and an *S*-configuration at C-3' of the phenylpyranone residue. The coupling constant of 1.2 Hz between the vinyl proton H-5' and the methine proton H-3' is indicative of a 90° dihedral angle between the C-5' – H-5' and C-3' – H-3' bonds, as observed for the five-membered structure (**3b**) of granatin A. The small coupling constant (0.6 Hz) between H-3' and H-2', corresponding to an approximately 90° dihedral angle between bonds C-3' – H-3' and C-2' – H-2', was ascribed to the *trans* relationship between these two protons,[11] indicating an *S*-configuration at C-2' of the phenylpyranone residue [Figure 3(b)]. The structure **6** shown in Figure 3 was thus assigned to this compound named davicratinic acid C.[14]

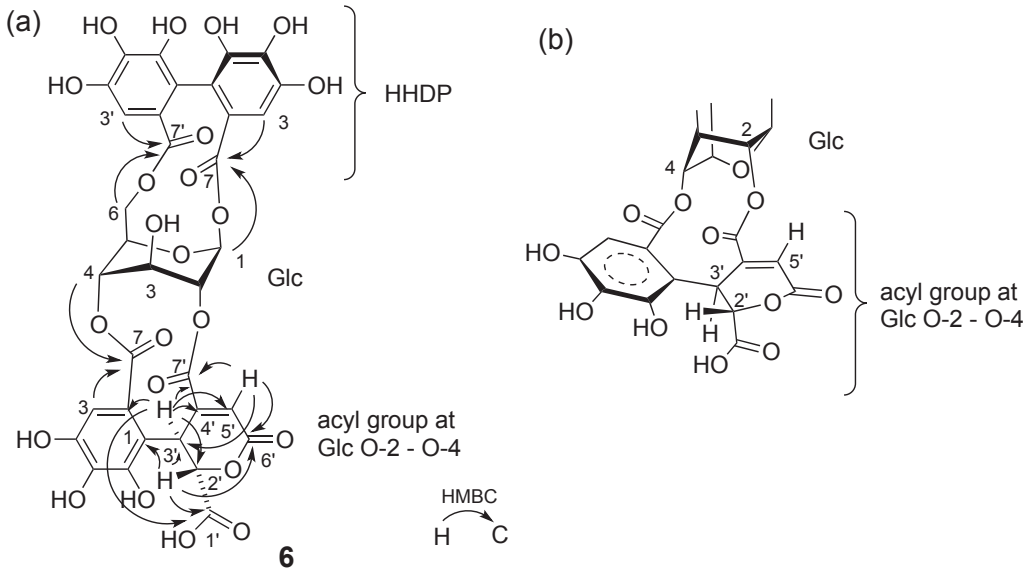

Figure 3. (a) Key HMBC correlations for compound **6**, indicating the locations of the acyl groups on the glucose (Glc) core. (b) Stereochemical relationships of protons H-2', H-3', and H-5' of the acyl group at Glc O-2 and O-4

The structures of the tannins reported in this paper are regarded as modified dehydroellagitannins structurally related to granatin A (**3**). Our preliminary study suggested the presence of further undescribed tannins. These studies will add to our knowledge of the metabolic diversity of hydrolysable tannins in plants.

EXPERIMENTAL

Optical rotations were recorded on the JASCO DIP-1000 digital polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on the Varian PS600 system (600 MHz for ^{1}H and 151 MHz for ^{13}C) using a mixture of acetone-d_6 and D_2O (9:1, v/v) as a solvent. Varian 400-MR ASW and Varian Mercury 300 instruments were also used for ^{1}H NMR measurements (400 and 300 MHz). Chemical shifts were adjusted based on

the chemical shifts of the solvent signals (δ 2.05 for ^{1}H, δ 29.8 for ^{13}C) and are provided as δ values from tetramethylsilane. CD spectra were measured on the JASCO J-7200W spectropolarimeter, using MeOH as the solvent. ESI-MS spectra were measured on the Bruker amaZon ETD/X spectrometer using a solvent of 50% MeCN containing 0.1% formic acid. HR-ESI-MS spectra were recorded on the Agilent HPLC-Chip/QTOF mass spectral system G6520+G4240. Analytical HPLC was performed on the YMC ODS-A column (4.6 mm i.d. × 150 mm) or YMC Triart C18 column (4.6 mm i.d. × 150 mm) using an eluant composed of 0.01 M H_3PO_4－0.01 M KH_2PO_4－MeCN (19:19:2, v/v/v) at 40 °C with a flow rate of 1.0 mL/min. A UV absorbance detector was used at 280 nm. Diaion HP-20 and MCI-gel CHP-20P (Mitsubishi Chemical), Toyopearl HW-40C and HW-40F (TOSOH), YMC gel ODS-A (YMC), and Sephadex LH-20 (GE Healthcare) were used for column chromatography. Sep-Pak C18 Plus cartridges (Waters) were used for purifying samples. A YMC-Pack ODS-A 324 (10 mm i.d.×300 mm) column or a YMC-Triart C18 (10 mm i.d. × 250 mm) column was used for preparative HPLC.

Isolation of ellagitannins from *D. involucrata* leaves. Dried leaves of *D. involucrata* (500 g), collected in May 2016, were homogenized in 70% acetone (three times, 10 L total). Concentrated filtrate (1 L) from the homogenate was extracted successively with $CHCl_3$, EtOAc, and *n*-BuOH. Each of the solvents was then evaporated, yielding $CHCl_3$ (14.7 g), EtOAc (13.5 g), and *n*-BuOH (43.4 g) extracts. The aqueous extract (77.6 g) which was obtained by concentrating the remaining aqueous solution was separated on a Diaion HP-20 column (10 cm i.d. × 45 cm) by gradient elution with increasing concentrations of MeOH in water (0 → 20 → 40 → 100%). A portion (7.1 g) of the 20% MeOH eluate (14.1 g) was further separated on a Toyopearl HW-40C column (2.2 cm i.d. × 73 cm) using 70% EtOH to give a fraction (1.17 g) containing tannins. Fractions with similar HPLC chromatograms (1.05 g from 6.95 g of the 20% MeOH eluate) were combined and then separated on an MCI-gel CHP-20P column (2.2 cm i.d. × 30 cm) using eluents of increasing concentrations of MeOH in water. A portion (167 mg) of the 10% MeOH eluate (792 mg) was further purified by preparative HPLC to produce helioscopinin B (**2**) (20.7 mg) and davicratinic acid A (**1**) (43.1 mg). The fraction (904 mg) from the Toyopearl column containing granatin A (**3**) was separated on an MCI-gel column (1.1 cm i.d. × 45 cm) with increasing concentrations of MeOH in water and further subjected to preparative HPLC to give purified **3** (42.1 mg). The fraction (2.52 g) containing **5** and **6** was separated on a Toyopearl HW-40F column (2.2 cm i.d. × 50 cm) and then on an MCI-gel column. Further purification by preparative HPLC yielded davicratinic acids B (**5**) (5.5 mg) and C (**6**) (16.3 mg).

A part (5.4 g) of the *n*-BuOH extract was subjected to a Diaion HP-20 column (3 cm i.d. × 35 cm) with increasing concentrations of MeOH in water, and the 20% MeOH eluate (873 mg) was purified on an

MCI-gel column (1.1 cm i.d. × 60 cm) using increasing concentrations of MeOH in water. The combined 10% MeOH and 15% MeOH eluates (303 mg) from the MCI-gel column was further separated on YMC-gel ODS-A and MCI-gel columns using increasing concentrations of MeOH in water. The fraction (101 mg) containing pedunculagin (**4**) was further purified on a Sephadex LH-20 column with 70% EtOH and then 70% acetone. Final purification by preparative HPLC yielded **4** (13.2 mg). Known compounds **1**–**4** were identified based on their ESI-MS spectra, and comparisons of their ^{1}H NMR spectral data with previously published data.

Davicratinic acid B (**5**). $[\alpha]_D$ -29.5 (*c* 1.0, MeOH). CD (MeOH) $[\theta]$ (nm): $[\theta]_{317}$ -1.5 × 10^4, $[\theta]_{284}$ +5.1 × 10^4, $[\theta]_{262}$ -2.3 × 10^4, $[\theta]_{242}$ +9.5 × 10^4, $[\theta]_{226}$ +1.6 × 10^5, $[\theta]_{200}$ -1.5 × 10^5. HR-ESI-MS *m/z* 818.0999 ($[M+NH_4]^+$) (Calcd for $C_{34}H_{24}O_{23}$+NH_4, 818.1047).

Davicratinic acid C (**6**). $[\alpha]_D$ +15.3 (*c* 1.0, MeOH). CD (MeOH) $[\theta]$ (nm): $[\theta]_{318}$ -0.9 × 10^4, $[\theta]_{284}$ +3.6 × 10^4, $[\theta]_{263}$ -1.5 × 10^4, $[\theta]_{237}$ +9.8 × 10^4, $[\theta]_{228}$ +1.2 × 10^5, $[\theta]_{200}$ -1.2 × 10^5. HR-ESI-MS *m/z* 823.0550 ($[M+Na]^+$) (Calcd for $C_{34}H_{24}O_{23}$+Na, 823.0600).

Treatment of granatin A (3) with Fe^{2+}/ascorbate. To a solution of granatin A (**3**) (12 mg) in 0.1 M phosphate buffer (pH 7.4) (4875 μL), 2 mM $FeSO_4 \cdot 7H_2O$ solution (1875 μL) and 50 mM sodium ascorbate solution (750 μL) were added. The mixture was kept at 37 ºC for 5.5 h and then acidified to pH 3 using 1 M HCl. The reaction mixture was then separated on a Sep-Pak C18 Plus cartridge by gradient elution with H_2O/MeOH. The 10% MeOH eluate was further purified by preparative HPLC to yield **5** (0.33 mg), which was identified by comparison of its HPLC retention time (15.45 min) with that of the same compound extracted from the leaves of *D. involucrata* and also by the $[M–H]^-$ ion peak at *m/z* 799.0651 in its HR-ESI-MS spectrum (Calcd for $C_{34}H_{24}O_{23}$–H, 799.0636).

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