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Research Paper

Chemical constituents of the leaves of *Aralia hiepiana*

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ABSTRACT: *Phytochemical study of the leaves of Aralia hiepiana, which is an endemic species of Lam Dong province, Vietnam, led to the isolation of six compounds, named quercetin-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside (**1**), rutin (**2**), ursolic acid (**3**), methyl 3,4 dihydroxybenzoate (**4**), methyl caffeate (**5**), and araliasaponin IV (**6**). Their structures were elucidated by 1D, 2D NMR and MS spectroscopic analyses in comparison with the data reported in the literature. These metabolites isolated for the first time from this species.*

KEYWORDS: *Aralia hiepiana, ursolic acid, methyl caffeate, rutin, quercetin-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside, araliasaponin IV.*

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I. INTRODUCTION

Aralia genus belongs to the Araliaceae family, consisting of 79 accepted species of deciduous or evergreen trees, shrubs, and rhizomatous herbaceous perennials, distributed in the Asia and America. Some Aralia species have been used in the treatment of respiratory inflammation, diabetes, cancer, liver protective and parasitic infections [1-7].

Aralia hiepiana J. Wen & Lowry, an endemic species of southern Vietnam was described and illustrated in 2002 [8]. In the previous report, five flavonoid compounds were isolated from the leaves of this species [9]. Continuing our research, six compounds **1-6** have been isolated for the first time from the leaves of *A. hiepiana*.

II. EXPERIMENTS

2.1. General experimental procedures

Column chromatography (CC) was performed on silica gel (Kieselgel 60, 70–230 mesh and 230–400 mesh, Merck, Darmstadt, Germany) and reversed-phase silica gel (ODS-A, 12 nm S-150 mm, YMC Co., Ltd., Japan) resins. TLC used pre-coated silica gel 60 F_{254} (1.05554.0001, Merck) and RP-18 F_{254S} plates (1.15685.0001, Merck), and compounds were visualized by spraying with aqueous 10% H_2SO_4 and heating for 3–5 min. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on an AVANCE III HD 500 (Bruker, Germany) FT-NMR spectrometer with tetramethylsilane (TMS) was used as an internal standard. ESI mass spectra were collected on Agilent 1100 LC/MS systems.

2.2. Plant material

The leaves of *A. hiepiana* were collected at Dalat, Lamdong, Vietnam in 2017 and identified by Dr. Nong Van Duy, Tay Nguyen Institute for Scientific Research, VAST. A voucher specimen (No.TN3/129) is deposited at the Herbarium of Tay Nguyen Institute for Scientific Research, VAST, Vietnam.

2.3. Extraction and isolation

The powdered leaves of *A. hiepiana* (4.5 kg) were extracted three times with methanol at room temperature and evaporated under low pressure to obtain 619 g residue. This residue was suspended in distilled water (2 L) and partitioned in turn with *n*-hexane, $CHCl_3$, and EtOAc to give corresponding extracts *n*-hexane (H, 187 g), $CHCl_3$ (C, 17 g), EtOAc (E, 52 g), and water layer (W, 2L).

The extract E (52 g) was separated on a silica gel chromatography column (CC), eluted with $CHCl_3$-MeOH (100:0 - 0:100, v/v) to yield five fractions, E1-E5. Fraction E4 (23 g) was fractioned on a silica gel CC eluted with CH_2Cl_2-acetone-MeOH (10:1:1, 5:1:1, 3:1:1, v/v/v) to give ten subfractions, E4.1-E4.10. Subfraction E.4.5 (5.4 g) was purified on a silica gel CC using CH_2Cl_2-acetone (6:1, v/v) to afford compound **3** (1.0 g). Fraction E5 (30 g) was separated on a silica gel CC with $CHCl_3$-MeOH (100:0 - 0:100, v/v) to get fourteen subfractions, E5.1-E5.14. Subfraction E5.6 (12 g) was separated on a silica gel CC with *n*-hexan-EtOAc (1:1, v/v) to furnish five subfractions, E5.6.1- E5.6.5. Subfraction E5.6.2 (504 mg) further purified on silica gel CC with CH_2Cl_2-acetone (15:1, v/v) followed by ODS-A CC with MeOH-H_2O (1:2.5, v/v) to give compound **4** (16 mg) and compound **5** (28 mg).

The W layer was passed through Diaion HP-20 CC using step-wise eluent of MeOH-H_2O (0:100, 25:75, 50:50, 75:25, and 100:0, v/v) to obtain four fractions W1-W4, after removal of the fraction eluted with 100% water. Fraction W2 (61 g) was separated on silica gel CC with a gradient mixture of $CHCl_3$-MeOH (100:0 - 0:100, v/v) to obtain ten fractions, W2.1-W2.10.

Fraction W2.6 (9.5 g) was furthur separated into ten subfractions, W2.6.1-W2.6.10, using silica gel CC with eluent EtOAc-MeOH-H_2O (30:10:2, v/v/v). Subfraction W2.6.10 (1.7 g) was passed through to Sephadex LH-20 CC with MeOH-H_2O (2:1, v/v), followed by silica gel CC with $CHCl_3$-MeOH (3:1, v/v), afforded compound **6** (15 mg).

Fraction W2.10 (6.8 g) was further applied to Sephadex LH-20 CC using a gradient of MeOH-H_2O (1:3 - 1:0, v/v) to obtain five subfractions. Subfraction W2.10.2 (5.0 g) was purified by silica gel CC with $CHCl_3$-MeOH (2:1 v/v), followed by ODS-A CC with MeOH-H_2O (1:1, v/v), yielding compounds **1** (10 mg) and **2** (5 mg).

Quercetin-3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside (**1**): Yellow powder, molecular formula $C_{27}H_{30}O_{16}$, ESI-MS: *m/z* 611 $[M+H]^+$ and *m/z* 609 $[M-H]^-$. ^1H NMR (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) see table 1.

Rutin (**2**): Light yellow powder, molecular formula $C_{27}H_{30}O_{16}$, ESI-MS: *m/z* 611 $[M+H]^+$ and *m/z* 609 $[M-H]^-$. ^1H NMR (500 MHz, CD_3OD) and ^{13}C NMR (125 MHz, CD_3OD) see table 1.

Ursolic acid (**3**): White amorphous powder, molecular formula $C_{30}H_{48}O_3$, ESI-MS: *m/z* 457.2 $[M+H]^+$ and *m/z* 455.3 $[M-H]^-$. ^1H-NMR (500 MHz, CD_3OD) δ_H 5.25 (1H, t, *J* = 3.5 Hz, H-12), 3.18 (1H, dd, *J* = 4.5, 11.0 Hz, H-3), 2.22 (1H, d, *J* = 11.0 Hz, H-18), 0.98 (3H, s, H-27), 0.99 (3H, s, H-23), 1.13 (3H, s, Hz, H-30), 0.98 (3H, s, H-25), 0.90 (3H, s, H-29), 0.87 (3H, s, H-26); 0.80 (3H, s, H-24). ^{13}C-NMR (125 MHz. CD_3OD) δ_C: 40.01 (C-1), 29.21 (C-2), 79.73 (C-3), 39.83 (C-4), 56.75 (C-5), 19.48 (C-6), 34.34 (C-7), 40.79 (C-8), 49.04 (C-9), 38.00 (C-10), 24.36 (C-11), 126.91 (C-12), 139.63 (C-13), 43.25 (C-14), 27.89 (C-15), 25.32 (C-16), 48.49 (C-17), 54.37 (C-18), 40.40 (C-19), 40.42 (C-20), 31.76 (C-21), 38.10 (C-22), 28.78 (C-23), 16.38 (C-24), 16.02 (C-25), 17.81 (C-26), 21.56 (C-27), 181.66 (C-28), 17.64 (C-29), 24.10 (C-30).

Methyl 3,4-dihydroxybenzoate (**4**): Brown amorphous powder, molecular formula $C_8H_8O_4$, ESI-MS: *m/z* 169.1 $[M+H]^+$. ^1H NMR (500 MHz, CD_3OD) δ_H: 7.44 (1H, d, *J* = 2.0 Hz, H-2), 7.43 (1H, dd, *J* = 2.0, 8.0 Hz, H-6), 6.81 (1H, d, *J* = 8.0 Hz, H-5), 3.84 (3H, s, -OCH_3). 13C NMR (125 MHz, CD_3OD) δ_C: 122.60 (C-1), 117.42 (C-2), 146.15 (C-3), 151.67 (C-4), 115.85 (C-5), 123.63 (C-6), 168.86 (C-7), 52.22 (OCH_3).

Methyl caffeate (**5**): White amorphous powder, molecular formula $C_{10}H_{10}O_4$, ESI-MS: *m/z* 195.1 $[M+H]^+$. ^1H NMR (500 MHz, CD_3OD) δ_H: 7.55 (1H, d, *J* = 16.0 Hz, H-7), 7.05 (1H, d, *J* = 2.0 Hz, H-2), 6.95 (1H, d, *J* = 2.0, 8.0 Hz, H-6), 6.79 (1H, d, *J* = 8.0 Hz, H-5), 6.26 (1H, d, *J* = 16.0 Hz, H-8), 3.77 (3H, s, -OCH3). ^{13}C NMR (125 MHz, CD_3OD) δ_C: 127.70 (C-1), 115.15 (C-2), 146.77 (C-3), 149.52 (C-4), 116.49 (C-5), 122.89 (C-6), 146.90 (C-7), 114.85 (C-8), 168.86 (C-9), 51.96 (OCH_3).

Araliasaponin IV (**6**)**:** White amorphous powder, molecular formula $C_{53}H_{86}O_{22}$, ESI-MS $[M+Na]^+$ at *m/z* 1098. ^1H NMR (500 MHz, pyridine-d_5): δ_H: 3.20 (1H, dd, *J* = 4.0, 11.0 Hz, H-3), 5.38 (1H, m, H-12), 3.13 (1H, dd, *J* = 3.5, 13.5 Hz, H-18), 1.20 (1H, s, H-23), 1.05 (1H, s, H-24), 0.80 (1H, s, H-25), 1.05 (1H, s, H-26), 1.20 (1H, s, H-27), 0.83 (1H, s, H-29), 0.83 (1H, s, H-30), 4.76 (1H, d, *J* = 7.5 Hz, H-1′), 5.37 (1H, d, *J* = 8.0 Hz, H-1″), 5.22 (1H, d, *J* = 8.0 Hz, H-1‴), 6.22 (1H, d, *J* = 8.0 Hz, H-1⁗). ^{13}C NMR (125 MHz, CD_3OD) δ_C: 38.63 (C-1), 28.07 (C-2), 89.32 (C-3), 39.50 (C-4), 55.78 (C-5), 18.38 (C-6), 32.35 (C-7), 39.74 (C-8), 47.87 (C-9), 36.69 (C-10), 23.24 (C-11), 122.73 (C-12), 144.00 (C-13), 42.00 (C-14), 26.48 (C-15), 23.48 (C-16), 46.89 (C-17), 41.59 (C-18), 46.09 (C-19), 30.59 (C-20), 33.83 (C-21), 32.96 (C-22), 27.66 (C-23), 16.34 (C-24), 15.38 (C-25), 17.29 (C-26), 25.94 (C-27), 176.49 (C-28), 32.96 (C-29), 23.62 (C-30). 105.20 (C-1′), 77.11 (C-2′), 84.77 (C-3′), 69.25 (C-4′), 75.75 (C-5′), 61.89 (C-6′), 104.63 (C-1″), 77.94 (C-2″), 78.43 (C-3″), 71.07 (C-4″), 66.76 (C-5″), 104.97 (C-1‴), 75.81 (C-2‴), 79.02 (C-3‴), 70.83 (C-4‴), 78.59 (C-5‴), 62.05 (C-6‴), 95.55 (C-1⁗), 73.77 (C-2⁗), 75.03 (C-3⁗), 71.25 (C-4⁗), 78.06 (C-5⁗), 62.17 (C-6⁗).

III. RESULTS AND DISCUSSION

Compound **1** was isolated as yellow powder. The molecular formula was established as $C_{27}H_{30}O_{16}$ by ESI-MS data ($[M+H]^+$ *m/z* 611 and $[M-H]^-$ *m/z* 609). The ^{1}H NMR spectrum showed the signals of two AX-type aromatic protons [δ_H 6.79 (d, *J* = 2.0 Hz, H-8) and 6.50 (d, *J* = 2.0 Hz, H-6)] and three protons of an ABX system [δ_H 7.86 (d, *J* = 2.5 Hz, H-2′), 7.65 (dd, *J* = 2.5, 8.5 Hz, H-6′), and 6.90 (d, *J* = 8.5 Hz, H-5′). Moreover, the signals of two anomeric protons at δ_H 5.59 (d, *J* = 1.5 Hz, H-1‴) and 5.25 (d, *J* = 8.0 Hz, H-1″) corresponded to two anomeric carbons at δ_C 99.93 and 105.04 were assigned to α-L-rhamnose (Rha) and β-D-glucose (Glc) units, respectively. The ^{13}C NMR and DEPT spectrum confirmed the presence of twenty seven carbons including one carbonyl carbon at δ_C 179.75 (C-4), nine quaternary carbons, seven methine carbons, eight oxymethin carbons, one oxymethylen carbon, and one methyl carbon. Therefore, the aglycon of **1** was identified as quercetin. The HMBC spectrum showed correlations between anomeric proton at δ_H 5.25 (H-1″) of Glc and carbon at δ_C 135.98 (C-3) of aglycon, between anomeric proton at δ_H 5.59 (H-1‴) of Rha and carbon at δ_C 163.68 (C-7), which suggest the glycosylation at C-3 and C-7 of quercetin skeleton. Based on data of ESI-MS, 1D, 2D NMR and compared with previous published data [10], the structure of **1** was determined as quercetin 3-O-β-D-glucopyranoside-7-O-α-L-rhamnopyranoside.

Compound **2** was also obtained as a yellow powder and its molecular formula, $C_{27}H_{30}O_{16}$, was determined by ESI-MS with a quasi-molecular ion peak at *m/z* 611 $[M+H]^+$. Its NMR data were similar to those of **1** (Table 1) including signals of quercetin, Rha, and Glc units. The ^{1}H NMR spectra of **2** also showed two anomeric proton signals at δ_H 5.13 (d, *J* = 7.5 Hz, H-1″) and 4.54 (d, *J* = 1.0 Hz, H-1‴) were assigned to α-L-rhamnose (Rha) and β-D-glucose (Glc) units, respectively. The position of attachment of the sugar moiety was obtained from the HMBC spectrum, in which correlations were seen between the anomeric proton of glucose H-(H-1″) and carbon of the aglycon (C-3). In addition, a cross-peak between the signal at δ_H 4.54 (H-1‴) and δ_C 68.56 (C-6″ of the glucose) confirmed that the glycosylation of the glucose unit by the rhamnose took place on the 6″-hydroxyl. Therefore, compound **2** was identified as rutin [11].

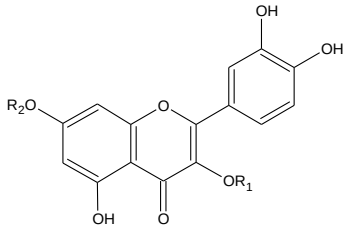
Table 1: The NMR data of **1** and **2**

	1		**2**	
Position	**δ_C**	**δ_H (*J* in Hz)**	**δ_C**	**δ_H (*J* in Hz)**
2	159.39		158.52	
3	135.98		135.63	
4	179.75		179.43	
5	162.83		162.99	
6	100.62	6.50 d. 2.0	99.96	6.23 d. 2.0
7	163.68		166.04	
8	95.56	6.79 d. 2.0	94.87	6.42 d. 2.0
9	158.1		159.34	
10	107.37		105.64	
1′	122.75		123.14	
2′	117.77	7.86 d. 2.5	117.70	7.69 d. 2.0
3′	145.89		145.85	
4′	150.17		149.81	
5′	116.17	6.90 d. 8.5	116.07	6.90 d. 8.5
6′	123.17	7.65 dd. 2.5. 8.5	123.56	7.65 dd. 2.0. 8.5
1″	105.04	5.25 d. 8.0	104.72	5.13 d. 7.5
2″	73.62	3.49 m	75.73	3.49 m
3″	75.06	3.57 m	78.20	3.44 m
4″	71.29	3.62 m	71.41	3.29 m
5″	77.26	3.49 m	77.23	3.35 m
6″	62.02	H_a:3.65 dd. 6.0; 11.0 H_b: 3.58 m	68.56	H_a: 3.82 dd. 1.0; 11.0 H_b: 3.41 m
1‴	99.93	5.59 d. 1.5	102.42	4.54 (d. 1.0)
2‴	70.09	3.87 m	72.11	3.66 m
3‴	71.71	4.04 m	72.25	3.56 dd
4‴	73.95	3.49 m	73.95	3.30 m*
5‴	73.17	3.83 m	69.71	3.47 m
6‴	18.05	1.27 d. 6.0	17.88	1.14 d. 6.0

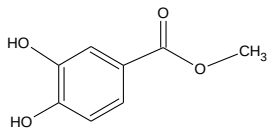
Compound **3** was obtained as white amorphous powder. The molecular formula was established as $C_{30}H_{46}O_3$ by ESI-MS data ($[M+H]^+$ *m/z* 457.2 and $[M-H]^-$ *m/z* 455.3). The ^{13}C NMR and DEPT spectrum indicated that **3** has total 30 carbons including seven methyls, nine methylens, six sp^3 methines, one sp^2 methine, five quaternary sp^3 carbons, and two quaternary sp^2 carbons. The three sp^2 carbons (δ_C 126.91, 139.63, and 181.66) indicated a double bond and carbonyl group of the ursane-type triterpenoid acid. The ^1H NMR spectrum also showed signals of seven methyl groups [δ_H 1.17 (s, H-23), 0.94 (s, H-24), 0.80 (s, H-25), 0.96 (s, H-26), 1.15 (s, H-27), 0.95 (s, H-29), 0.89 (s, H-30)], one trisubstituted olefin [δ_H 5.42 (dd, *J* = 4.0, 8.5 Hz, H-12)], and one oxymethine [δ_H 3.18 (dd, *J* = 4.5, 11.0 Hz, H-3)]. Furthermore, HMBC correlations observed from H-2 to C-1, C-3, and C-4, from H-3 to C-4, C-23, and C-24, from H-11 to C-12 and C-13, from H-29 to C-19, from H-30 to C-20, and from H-18 and H-16 to C-28 allowed to confirm the structure of **3**. Based on NMR spectroscopic data combined comparison with literature data [12] the structure of 3 was established as ursolic acid.

Compound **4** was obtained as brown amorphous powder. The ^1H NMR spectra showed the signals of three protons in 1,3,4-trisubstituted bezene ring at δ_H 7.44 (1H, d, *J* = 2.0 Hz, H-2), 7.43 (1H, dd, *J* = 2.0, 8.0 Hz, H-6), and 6.81 (1H, d, *J* = 8.0 Hz, H-5) and the signal at δ_H 3.84 (3H, s) of a methoxy group in the structure. The ^{13}C NMR and DEPT spectrum confirm the presence of eight carbons including one carbonyl carbon at δ_C 168.86, two oxygenated aromatic carbons at δ_C 146.15 and 151.67, four other aromatic protons at δ_C 123.63, 122.6, 117.42, and 115.85, and one methoxy carbon at δ_C 52.22. Thus, compound **4** was recognized as 3,4 dihydroxybenzoic methyl ester with molecular formula $C_8H_8O_4$ based on the spectral data and the literature [13].

Compound **5** was obtained as a white amorphous powder. The structure of **5** very similar with the structure of 4 except for the presence of the olefinic signal at δ_H 7.55 (1H, d, *J* = 16.0 Hz, H-7) and 6.26 (1H, d, *J* = 16.0 Hz, H-8). The ^1H NMR spectrum also revealed signals in a 1,3,4-trisubstituted benzene ring at δ_H 7.05 (1H, d, *J* = 2.0 Hz, H-2), 6.95 (1H, d, *J* = 2.0, 8.0 Hz, H-6), and 6.79 (1H, d, *J* = 8.0 Hz, H-5)] and one methoxy group at δ_H 3.77 (3H, s). The ^{13}C and DEPT spectrum confirmed ten signals include five methin carbons, four quaternary carbons and one methoxy group. In the HMBC spectrum data determined the correlation between the proton of olefinic with C-2 (δ_C 127.7) of benzene ring, (H-1'/C-2, C-3, C-4, C-5) and H-2'/C-2, C-1', C-3'). From the above spectral data and compared with the literature [14], compound **5** was indentified as methyl caffeate with its molecular formula being $C_{10}H_{10}O_4$.



(1) R_1: Glc, R_2: Rha
(2) R_1: Glc-(1→6)-Rha, R_2: H



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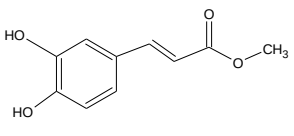

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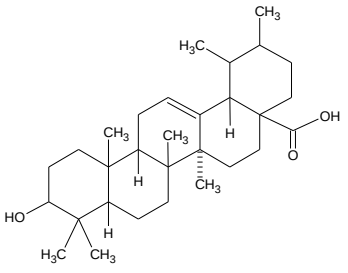

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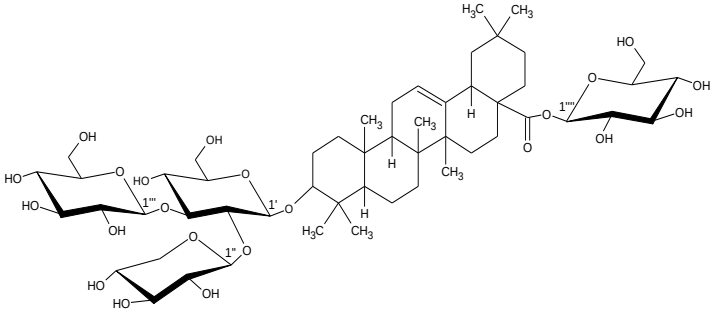

(6)

Figure 1: The structure of six compounds (**1-6**)

Compound **6** was isolated as a white amorphous powder. The ^1H NMR spectrum showed the presence of seven singlet methyl protons δ_H 1.20, 1.05, 0.83 (each 6H, s), 0.80 (3H, s), a trisubstituted olefinic proton (δ_H 5.38 m, H-12) which was characteristic of olean-type triterpene skeleton and four anomeric proton signals [(δ_H 4.76 d, *J* = 7.5 Hz, H-1′), (δ_H 5.37, d, *J* = 8.0 Hz, H-1″), (δ_H 5.22, d, *J* = 8.0 Hz, H-1‴), and (δ_H 6.22, d, *J* = 8.0 Hz)] of the sugar moieties. The ^{13}C NMR spectrum showed the presence of an ester carbonyl carbon (δ_C 176.46 (C-28) and five anomeric carbon signals [(δ_C 105.20 (Glu, C-1′), 104.63 (Xyl, C-1″), 104.97 (Glu, C-1‴), and 95.55 (Glu, C-1⁗)]. In the HMBC, the correlations were observed between the proton signal at δ_H 4.76 (Glu, H-1′) to the carbon signal at δ_C 89.32 (C-3) of the aglycon and between the anomeric proton signal at δ_H 5.37 (Xyl,

H-1″) and the carbon signal at δ_C 77.11 (Glu-C-2′), the anomeric proton signal at δ_H 5.22 (Glu, H-1‴) and the carbon signal at δ_C 84.77 (Glu-C-3'). In addition, an anomeric proton at δ_H 6.22 (Glu-1⁗) showed the correlation with the carbon signal at δ_C 176.46 (C-28) which suggested glycosylation at C-3 of aglycon with a ([xyl-(1→2)]-[glc-(1→3)]-glc) moiety and at C-28 with a glucose unit. Accordingly, the structure of **6** was elucidated as araliasaponin IV, which was isolated from *A. decaisneana* [15] and *Catunaregam spinosa* [16].

IV. CONCLUSION

From the leaves of *A. hiepinana* using combined chromatographic methods obtained six compounds, including quercetin-3-O-β-D-glucopyranoside-7-O-α-L-rhampyranoside, rutin, ursolic acid, methyl 3,4 dihydroxybenzoate, methyl caffeate, and araliasaponin IV. These structures were elucidated by 1D, 2D NMR, and mass spectrum. All of them were isolated for the first time from this plant.

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