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Research Article

Chemical Constituents from *Thalictrum ramosum*

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Abstract

Thalictrum ramosum is a plant from *Thalictrum genus*, and is also one substitute of Coptidis Rhizoma in Chinese folk medicine. Phytochemical investigation on the EtOH extract of *T. ramosum* led to the isolation of 9 compounds. Their structures were elucidated as berberine (1), columbamine (2), thalidastine (3), magnoflorine (4), 1-(4-hydroxy-3-methoxy)-phenyl-2-[4-(1,2,3-trihydroxy-propyl)-2-methoxy]-phenoxy-1,3-propandiol (5), citroside B (6), glochidionionoside A (7), apigenin 6,8-di-C-β-D-xylopyranoside (8) and hydrangeifolin I (9) through 1D and 2D NMR, MS experiments and comparison with literature data. All compounds are isolated from this plant for the first time.

Keywords: Alkaloid; Flavone C-glycoside; Lignan; Megastigmane glucoside; *Thalictrum ramosum*

Introduction

Thalictrum often refers to the plants form *Thalictrum* genus which has been used in Tibetan medicine and Mongolian medicine in China for thousands of years. It was found that 29 plants from *Thalictrum* genus were used as folk medicine in China and 14 of them were used as the succedaneum of Coptidis Rhizoma (Huanglian in Chinese) [1]. The *Thalictrum* herbs were also called 'maweihuanglian' or 'mawei lian' (mawei in Chinese means horsetail) because they have a horsetail-like appearance and anti-inflammation and antibacterial functions resembling to Coptidis Rhizoma. Modern pharmacological investigations revealed that the important associations of *Thalictrum* with the bioactivities of antitumor, anti-inflammation, antivirus, and effects on the cardio-vascular, autoimmune and central nervous system, etc [2-3]. Some secondary metabolites including alkaloids, triterpenes, flavonoids, steroids and organic acids have been reported from plants of *Thalictrum* genus [3-7].

T. ramosum, is one of the substitutes of Coptidis Rhizoma. Recently, we reported some cycloartane triterpene saponins from the plants in *Thalictrum* genus including this herb [1-3]. Further phytochemical investigations on the n-BuOH-soluble fraction of the EtOH extract of *T. ramosum* has led to the purification of 9 compounds and their structures were elucidated as: berberine (1), columbamine (2), thalidastine (3), magnoflorine (4), 1-(4-hydroxy-3-methoxy)-phenyl-2-[4-(1,2,3-trihydroxy-propyl)-2-methoxy]-phenoxy-1,3-propandiol (5), citroside B (6), glochidionionoside A (7), apigenin 6,8-di-C-β-D-xylopyranoside (8), hydrangeifolin I (9) by means of UV, IR, MS, NMR, HMBC, HSQC, ^{1}H-^{1}H COSY, ROESY, etc.

Experimental

General experimental procedures

HR-ESI-MS measurements were carried out on an Agilent series 1200SL HPLC (Agilent Technologies, USA). NMR spectra were recorded on Bruker Avance-300, 400, 500 and 600 spectrometers. Prep-HPLC purification was carried out on a Cosmosil 5C18-AR-II column (250mm × 20 mm i.d., 5mm, Cosmosil, Japan) on a Shimadzu LC-20AP Series prep-HPLC apparatus (Shimadzu, Japan). Column chromatography was performed on ODS (Alltech, USA), silica gel (200 - 300 mesh, Qingdao Marine Chemical Group Co., Qingdao, China), Macroporous resin (D101, Haiguang Chemical Group Co., Tianjin, China), Sephadex LH-20(Pharmacia, USA). The solvents of analytical grade, used for extraction, gel chromatography and macroporous resin column chromatography, were supplied by Kaitong Chemical Co. Ltd. (Tianjin, China). Solvents applied for preparative column and HPLC analysis were of HPLC grade and purchased from Merck (Darmstadt, Germany). Distilled water was purified with a Millipore Milli Q-Plus system (Millipore, Milford, MA, USA).

Plant material

The rhizomes of *T. ramosum* Boivin were collected from Emei, Sichuan Province, China in 2012, and authenticated by Dr. Chun-Feng Qiao. A voucher specimen was deposited in Institute of Traditional Chinese Medicine, Guangdong Food and Drug Vocational College.

Isolation and purification

Dried plants of *T. ramosum* were powdered and extracted with 95% ethanol (3 × 20L) under reflux. The ethanol extract was suspended in water and then successively extracted with petroleum ether, EtOAc and n-BuOH.

The n-BuOH solution was concentrated and gives a residue (344 g), which was separated by a silica gel column using $CHCl_3$-MeOH

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(1:0 → 1:1) as eluent, affording 14 fractions (Fr. 1-14). Compound 1 was obtained by recrystallization of Fr. 7. Fr. 8 (8.6 g) was purified by a silica gel column using EtOAc-MeOH (10:1→5:1) as eluent to afford Fr. 8.1 - Fr. 8.7 (0.7 g). The same elution method was applied to Fr. 8.7 to afford Fr. 8.7.1 which was further purified by Sephadex LH-20 chromatography with MeOH to afford compound 2 (2.6 mg). Fr. 12 was purified by an ODS chromatographic method eluted with MeOH-Water (10%→90%) to afford Fr. 12.1 - Fr. 12.4. Fr. 12.3 was further purified by Sephadex LH-20 chromatography using MeOH-Water (90:10) as eluent to afford Fr. 12.1 - Fr. 12.3. Compound 4 (22.5 mg) and 9 (24.1 mg) was isolated from Fr. 12.3.3 by Prep-HPLC using CH_3CN-H_2O (15:85) as eluent.

Fr. 9 (25 g) was purified by a silica gel column using $CDCl_3$-MeOH (10:1→1:1) as eluent to afford Fr. 9.1 - Fr. 9.7. Fr. 9.6 was purified by an ODS chromatographic method using MeOH-Water (10% → 90%) as eluent to afford Fr. 9.6.1 - Fr. 9.6.3. Prep-HPLC was applied to Fr. 9.6.2 using CH_3CN-H_2O (25:75) as eluent to afford compound 3 (50 mg). Fr. 9.5 was purified by an ODS chromatographic method using MeOH-Water (10% → 90%) and then further purified by Sephadex LH-20 chromatography using MeOH-H_2O (90:10) as eluent to afford Fr. 9.5.1.1 and Fr. 9.5.1.2. Prep-HPLC was applied to Fr. 9.5.1.1 using CH_3CN-H_2O (18:82) as eluent to afford compound 6 (12.1 mg) and **7** (2.0 mg). Compound 5 (10.1 mg) was isolated from Fr. 9.5.1.2 by Prep-HPLC using CH_3CN-H_2O (13:87) as eluent. Fr-14 was chromatographedon a macropourous resin column using EtOH-Water (0% → 95%) as eluent to afford Fr. 14. 1 - Fr. 14.6. Fr. 14.4 was purified by an ODS chromatographic method using MeOH-Water (10% → 90%) as eluent to afford Fr. 14.4.1 - Fr. 14.4.6. Prep-HPLC was applied to Fr. 14.4.5 using CH_3CN-H_2O (12:88) as eluent to afford compound 8.

Results and Discussion

Chemical study on *T. ramosum* led to the isolation of nine compounds including four alkaloids, one lignans, two megastigmane glucosides, one flavone C-glycoside and a benzylated disaccharide. And their structures were characterized as follows.

Compound 1 yellow crystals: $C_{20}H_{18}NO_4^+$, ESI-MS m/z336 $[M]^+$,^{1}H -NMR (DMSO-d6, 400 MHz) δ:9.87 (1H, s, H-8), 8.91 (1H, s, H-13), 8.19 (1H, d, J = 9.1 Hz, H-11), 7.98 (1H, d, J = 9.1 Hz, H-12), 7.77 (1H, s, H-1), 7.08 (1H, s, H-4), 6.17 (2H, s, OCH_2O), 4.93 (2H, t, J = 6.2 Hz, H-6), 4.10 (3H, s, 9-OCH_3), 4.07 (3H, s, 10-OCH_3), 3.21 (2H, t, J = 6.2 Hz, H-5). ^{13}C NMR (DMSO, 100 MHz) δ: 150. 4 (C-10), 149.8 (C-3), 147.7 (C-2), 145.4 (C-9), 143.7 (C-8), 137.5 (C-14), 133.0 (C-12a), 130.6 (C-4a), 126.8 (C-11), 123.5 (C-12), 121.4 (C-8a), 120.4 (C-14a), 120.1 (C-13), 108.4 (C-4), 105.4 (C-1), 102.5 (OCH_2O), 61.9 (9-OCH_3), 57.0 (10-OCH_3), 55.2 (C-6), 26.3 (C-5). These data were consistent those of berberine in the literature [8]. Thus, compound 1 was elucidated as berberine.

Compound 2 yellow powder: ^{1}H NMR (CD_3OD, 400 MHz) δ: 9.74 (1H, s, H-8), 8.63 (1H, s, H-13), 8.09 (1H, d, J = 9.1 Hz, H-11), 7.99 (1H, d, J = 9.1 Hz, H-12), 7.55 (1H, s, H-1), 7.01 (1H, s, H-4), 5.95 (2H, m, H-6), 4.20 (3H, s, 9-OCH_3), 4.10 (3H, s,10-OCH_3) 3.96 (3H, s, 2-OCH_3), 3.23 (2H, m, H-5). ^{13}C NMR (CD_3OD, 100 MHz) δ: 152.5 (C-9), 151.9 (C-2), 148.3 (C-3), 146.3 (C-8), 145.7 (C-10), 140.0 (C-13a), 135.3 (C-12a), 128.5 (C-4a), 128.1 (C-12), 124.4 (C-11), 123.3 (C-14), 121.1 (C-13), 120.7 (C-8a), 113.2 (C-4), 112.0 (C-1), 62.5 (9-OCH_3), 57.7 (10-OCH_3), 57.5 (3-OCH_3), 56.7 (C-6), 27.8 (C-5). These data were consistent those of columbamine in the literature [9]. Compound 2 was elucidated as columbamine.

Compound 3 yellow powder: ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.89 (1H, br s, H-8), 8.97 (1H, s, H-13), 7.90 (1H, br s, H-11), 7.90 (1H, br s, H-12), 7.85 (1H, s, H-1), 7.16 (1H, s, H-4), 6.20 (2H, s, OCH_2O), 5.11 (1H, d, J = 13.0 Hz, H-5), 5.01 (1H, br s, H-6a), 4.84 (1H, d, J = 13.0 Hz, H-6b), 4.08 (3H, s, 9-OCH_3). ^{13}C NMR (DMSO -d_6, 75 MHz) δ: 149.7 (C-3), 149.6(C-10), 148.6 (C-2), 145.0 (C-8), 141.3(C-9), 136.4 (C-14), 132.6 (C-12a), 132.2 (C-11), 131.3 (C-4a), 123.7 (C-12), 122.4 (C-8a), 120.5 (C-14a), 119.8 (C-13), 108.1 (C-4), 105.4 (C-1), 102.3 (OCH_2O), 61.4 (C-6), 62.9 (9-O CH_3), 60.8 (C-5). These data were consistent those of thalidastine in the literature [10]. So, compound 3 was elucidated as thalidastine.

Compound 4 yellow amorphous powder: $C_{20}H_{24}NO_4^+$, ESI-MS m/z 342 $[M+H]^+$, ^{1}H NMR (CD_3OD, 300 MHz) δ : 6.63 (1H, d, J = 7.2 Hz, H-9), 6.40 (1H, d, J = 7.2 Hz, H-8), 6.40 (1H, br s, H-3), 3.81 (3H, s, 10-OCH_3), 3.72 (3H, s, 2-OCH_3), 3.68 (1H, m, H-6a), 3.38 (1H, m, H-5β), 3.18 (3H, br s, N-OCH_3β), 3.06 (1H, m, H-4α), 2.90 (1H, m, H-5α), 2.85 (1H, m, H-7β), 2.72 (3H, br s, N-OCH_3α), 2.48 (1H, m, H-4β), 2.30 (1H, m, H-7α). ^{13}C NMR (CD_3OD, 75 MHz) δ : 153.0 (C-2a), 151.7 (C-10), 150.7 (C-1), 149.7 (C-11), 126.0 (C-7a), 123.5 (C-11a), 123.4 (C-11b), 121.0 (C-6b), 117.0 (C-8), 115.8 (C-3a), 110.5 (C-9), 109.3 (C-3), 70.9 (C-6a), 62.2 (C-5), 56.3 (2-OCH_3), 55.9 (10-OCH_3), 53.8 (N-CH_3α), 43.5 (N-CH_3β), 31.6 (C-7), 24.6 (C-4). The above spectral data were identical to those of magnoflorine reported in the reference [8]. Thus compound 4 was determined to be magnoflorine.

Compound 5 amorphous light-yellowish powder: $C_{20}H_{26}O_9$, ESI-MS m/z 433$[M+Na]^+$, ^{1}HNMR (CD_3OD, 500 MHz) δ : 7.04 (1H, d, J = 1.8 Hz, H-2), 7.02 (1H, d, J = 1.7 Hz, H-2′), 6.90 (1H, d, J = 8.2 Hz, H-5′), 6.85 (1H, dd, J = 8.2, 1.6 Hz, H-6′), 6.84 (1H, dd, J = 8.2, 1.6 Hz, H-6), 6.74 (1H, d, J = 8.1 Hz, H-5), 4.84 (1H, d, J = 5.8 Hz, H-7), 4.56 (1H, d, J = 6.0 Hz, H-7′), 4.36 (1H, dt, J = 5.7, 3.8 Hz,H-8), 3.87 (1H, dd, J = 12.0, 3.7 Hz, H-9a), 3.83 (3H, s, 3-OMe), 3.83 (3H, s, 3′-OMe), 3.80 (1H, dd, J = 12.0, 3.7 Hz,H-9b), 3.67 (1H, dt, J = 5.9, 4.1 Hz,H-8′), 3.50 (1H, dd, J = 11.2, 4.0 Hz, H-9′a), 3.38 (1H, dd, J = 11.2, 4.1 Hz,H-9′b); ^{13}C NMR (CD_3OD, 500 MHz) δ: 151.7 (C-3′), 148.7 (C-3), 148.6 (C-4′), 147.0 (C-4), 137.7 (C-1′), 134.2 (C-1), 121.0 (C-6), 120.5 (C-6′), 118.7 (C-5′), 115.6 (C-5), 112.3 (C-2′), 111.8 (C-2), 86.2 (C-8), 77.4 (C-8′), 75.1 (C-7′), 74.1 (C-7), 64.2 (C-9′), 62.2 (C-9), 56.5 (3′-OCH_3), 56.3 (3-OCH_3). These data were consistent those in the literature [11]. Therefore, compound 5 was elucidated as 1-(4-hydroxy-3-methoxy)-phenyl-2-[4-(1,2,3-trihydroxy-propyl)-2-methoxy]-phenoxy-1,3-propandiol.

Compound 6 amorphous powder: $C_{19}H_{30}O_8$, ESI-MS m/z 409 $[M+Na]^+$,^{1}H NMR (Pyridine-d_5, 500 MHz) δ : 6.04 (1H, s, H-8), 5.14 (1H, d, J = 7.7 Hz, H-1′), 5.10 (1H, m, H-3), 4.48 (1H, dd, J = 11.5, 2.2 Hz, H-6′a), 4.31 (1H, dd, J = 11.5, 5.3 Hz, H-6′b), 3.99 (1H, t, J = 8.1 Hz, H-2′), 3.62 (1H, s), 3.04 (1H, dd, J = 13.6, 2.0 Hz, H-4a), 2.30 (1H, dd, J = 12.5, 2.4 Hz, H-2a), 2.23 (3H, s, H-10), 1.79 - 1.72 (2H, m, H-2b,4b), 1.70 (3H, s, H-13), 1.69 (3H, s, H-12) and 1.21 (3H, s, H-11). ^{13}C NMR (Pyridine-d_5, 125 MHz) δ : 212.0 (C-7), 198.1 (C-9), 119.3 (C-6), 101.4 (C-1′), 99.0 (C-8), 79.7 (C-5), 78.7 (C-3′), 78.7 (C-5′), 75.7 (C-2′), 72.2 (C-4′), 63.3 (C-3), 63.0 (C-6′), 50.8 (C-2), 47.9 (C-4), 36.9 (C-1), 32.8 (C-12), 30.3 (C-11), 27.6 (C-10) and 27.0 (C-13). These data were consistent those in the literature [12]. Compound 6 was elucidated as citroside B.

Compound 7 pale yellow amorphous powder: ^{1}H NMR (DMSO -d_6, 600 MHz) δ : 6.03 (1H, dd, J = 15.6 Hz, H-7), 5.75 (1H, s, H-4),

5.71 (1H, dd, J = 15.5, 6.1 Hz, H-8), 4.98 (2H, s, H-13), 4.32 (1H, m, H-9), 4.13 (1H, d, J = 7.8 Hz, H-1′), 2.55 (1H, d, J = 16.6 Hz, H-2a), 2.05 (1H, d, J = 16.4 Hz, H-2b), 1.82 (3H, d, J = 1.3 Hz, H-10), 0.94 (3H, s, H-11), 0.92 (3H, s, H-12). ^{13}C NMR (DMSO-d_6, 150 MHz) δ : 200.8 (C-3), 166.9 (C-5), 132.6 (C-7), 131.3 (C-8), 127.0 (C-4), 104.5 (C-1′), 80.0 (C-6), 77.9 (C-5′), 77.8 (C-3′), 75.1 (C-2′), 74.8 (C-13), 72.0 (C-9), 71.5 (C-4′), 62.7 (C-6′), 50.7 (C-2), 42.4 (C-1), 23.5 (C-11), 24.6 (C-12) and 19.7 (C-10). These data were consistent those in the literature [13]. Compound 7 was elucidated as glochidionionoside A.

Compound 8 yellow powder: ^{1}H NMR (DMSO-d_6, 500 MHz) δ : 13.76 (1H, s, 5-OH), 7.95 (2H, d, J = 8.8 Hz, H-2′, 6′), 6.93 (2H, d, J = 8.8 Hz, H-3′,5′), 6.81 (1H, s, H-3), 4.87 (1H, d, J = 6.8 Hz, H-1), 4.63 (1H, d, J = 9.7 Hz, H-1‴). ^{13}C NMR (DMSO-d_6, 125MHz) δ : 163.6 (C-2), 102.6 (C-3), 182.1 (C-4), 161.2 (C-7), 121.5 (C-1′), 128.6 (C-2′, 6′), 115.9 (C-3′, 5′), 159.5 (C-4′), 75.2 (C-1″), 71.4 (C-2″), 78.7 (C-3″), 69.7 (C-4″), 70.5 (C-5″), 74.6 (C-1‴), 70.9 (C-2‴), 78.8 (C-3‴), 69.9 (C-4‴) and 70.3 (C-5‴). These data were consistent those in the literature [14]. Compound 8 was elucidated as apigenin 6,8-di-C-β-D-xylopyranoside.

Compound 9 pale yellow amorphous powder: $C_{19}H_{28}O_{10}$, m/ z 439 $[M+Na]^+$, ^{1}H NMR (CD_3OD, 300 MHz) δ : 7.38 (2H, d, J = 6.7 Hz, H-2, 6), 7.30 (2H, m, H-3, 5), 7.23 (1H, m, H-4), 4.75 (1H, d, J = 11.8 Hz, H-7a), 4.82 (1H, s, H-1’’), 4.60 (1H, d, J = 11.8 Hz, H-7b), 4.29 (1H, d, J = 7.6 Hz, H-1’), 3.96 (1H, dd, J = 11.2 Hz, H-6’b), 3.84 (1H, m, H-6’a), 1.23 (3H, d, J = 6.2 Hz, H-6’’). ^{13}C NMR (CD_3OD, 75 MHz) δ : 138.8 (C-1), 129.3 (C-2, 3, 5, 6), 128.8 (C-4), 103.1 (C-1’), 102.3 (C-1’’), 78.0 (C-3’), 76.9 (C-5’), 75.1 (C-2’), 74.0 (C-4’’),72.3 (C-3’’), 72.2 (C-2’’),71.8 (C-7), 71.7 (C-4’), 69.8 (C-5’’), 68.1 (C-6’) and 18.1 (C-6’’). These data were consistent those in the literature [15]. So, compound 9 was elucidated as hydrangeifolin I (Figure 1).

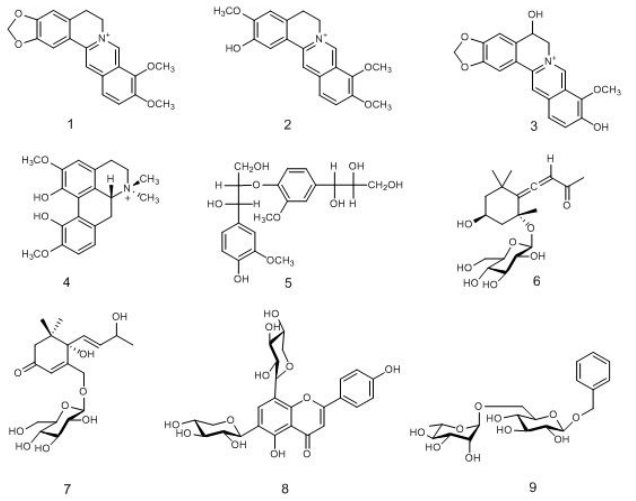

Figure 1: Structures of compounds 1-9.

Even though *Thalictrum* showed different morphological features from Coptidis Rhizoma, many *Thalictrum* plants have a very close name to Coptidis Rhizoma (horsetail-Coptidis-Rhizoma) and were used as the succedaneum of Coptidis Rhizoma for the treatment of inflammation and infectious diseases for thousands years in China. As is known, bioactivities and functions of herbal medicine are closely related with its chemical composition. The phytochemical investigation in current study and reported literatures showed that the plants of those two genera (*Thalictrum* and *Copdis*) contain some same constituents such as berberine-type alkaloid [16-18]. Berberine-type alkaloids showed potent anti-inflammatory and antibacterial activities [19-23]. Compounds berberine (1), columbamine (2) and magnoflorine (3) has also been reported from Coptidis Rhizoma before [10]. Those compounds occurrence in both genera led them to have some same functions and explained why those *Thalictrum* plants were used as the substitute of Coptidis Rhizoma for the treatment of inflammatory and infectious diseases. Furthermore, together with *Thalictrum* genus, *Coptis* genus, the source of Coptidis Rhizoma, also belongs to the subfamily *Thalictroideae*. Researches on the chemical composition and pharmacological activities should be beneficial for the further development and application of *T. ramosum* and other plants of *Thalictrum* genus.

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