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ORIGINAL ARTICLE

Phytochemical Profile of the Aerial Parts of *Rehmannia glutinosa* Liboschitz var. *purpurea* Makino

Huu Tung Nguyen[1,2], Thi Ngan Dang[1,3], Takuhiro Uto[4], Tomoe Ohta[4], Hitoshi Watanabe[5], Yukihiro Shoyama[4]

[1]Faculty of Pharmacy, Phenikaa University, [2]Phenikaa Research and Technology Institute (PRATI), A&A Green Phoenix Group, 167 Hoang Ngan, [3]School of Medicine and Pharmacy, Vietnam National University, Hanoi, Vietnam, [4]Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, Nagasaki International University, Nagasaki, [5]Center of Environment, Health and Field Science, Chiba University, Ciba City, Chiba, Japan

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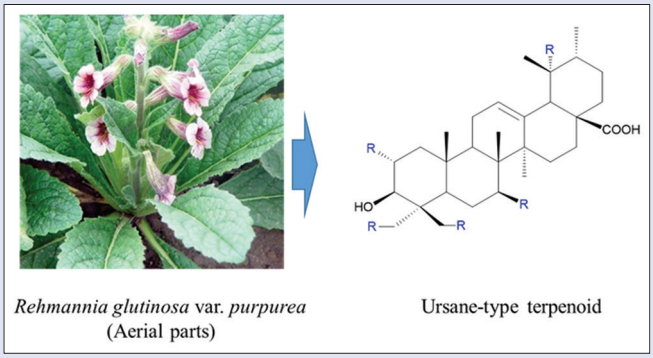
ABSTRACT

Background: The roots of *Rehmannia glutinosa* (RG) or Rehmanniae Radix are a well-known medicinal material in the Oriental medicine, and its phytochemical profile has been extensively studied with more than 100 individual compounds from *Rehmannia* species. In contrast, bioactive components of the aerial part of the title plant are largely unknown as only several compounds reported up to date. **Objective:** The objective was to study on chemical constituents of the aerial parts of the title plant and evaluate the aerial parts as a supplementary source for Rehmanniae radix. **Materials and Methods:** Solvent extraction, partition, and column chromatography was used to separate individual compounds; spectroscopic data including nuclear magnetic resonance and mass spectrometry were analyzed to determine the chemical structure of the isolates. **Results:** Eight compounds including five ursane-type triterpenoids for the first time from RG (ursolic acid [1], pomolic acid [2], 2β-hydroxypomolic acid [3], asiatic acid [4] and 7β,24-dihydroxy ursolic acid [5]) and three main glycosides (ajugol [6], aucubin [8], and acteoside [7]) were characterized from the aerial parts of the title plant. Their structures were identified on the basis of spectroscopic data and comparison with those reported in the literature. **Conclusion:** The current study reveals various ursane triterpenes in the organic portion beside the main hydrophilic glycosides in the RG aerial parts. The occurrence of various ursane triterpenes contributed in part to phytochemical database and evidence of the biological activity associated with potential in use as a medicinal material of the RG leaves.

Key words: *Rehmannia glutinosa* var. *purpurea*, *Rehmannia glutinosa*, Rehmanniae Radix, triterpene, ursane

SUMMARY

- *Rehmannia glutinosa* (RG) is one of the most well-known and used in the Oriental medicine
- Eight compounds including five ursane-type triterpenoids for the first time from RG (ursolic acid [1], pomolic acid [2], 2β-hydroxypomolic acid [3], asiatic acid [4], and 7β,24-dihydroxy ursolic acid [5])
- The presence of various ursane triterpenes in the RG leaves contributed in part to phytochemical database and evidence of the pharmacological benefit supporting potential as a medicinal material.



Abbreviations used: DEPT: Distortionless Enhancement by Polarization Transfer; EtOAc: Ethyl acetate; LC: Liquid Chromatography; MeOH: Methanol; MS: Mass Spectrometry; NMR: Nuclear Magnetic Resonance; RG: *Rehmannia glutinosa*; RP: Reversed-Phase.

Correspondence:

Dr. Huu Tung Nguyen,
Faculty of Pharmacy, Phenikaa University, Hanoi, Vietnam.
E-mail: tung.nguyenhuu@phenikaa-uni.edu.vn

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INTRODUCTION

Rehmannia glutinosa (RG) including RG var. *purpurea*, commonly known as Di-huang in Chinese, is a perennial herb belonging to the Scrophulariaceae family, and Rehmanniae Radix is one of the important herbs in the traditional Chinese medicine prescribed with other herbal medicines for diabetes, anemia, hemoptysis, and gynecological diseases. Phytochemical profile of *Rehmannia* species roots has been intensively studied and includes more than 100 individual compounds mainly iridoids, i.e., catalpol, geniposide, aucubin, and rehmanniosides A–D,[1-3] along with several sesquiterpenes,[4-6] phenylethanoid glycosides,[7,8] flavonoid,[9] and triterpene[10]. In addition, up-to-date biological study on the title medicinal herb revealed significant pharmacological properties of anticancer,[11,12] anti-inflammation,[13] antidiabetes,[14,15] hepatoprotection,[16,17] and antiosteoporosis,[18] respectively. However, chemical composition and biological activities of the aerial part of RG are largely unknown since very few phytochemical studies of the RG leaves have been reported yet.[19,20]

Previously, we succeeded to set up the micropropagation method[21] resulting in virus-free plants by tip tissue culture and differences between plants infected with virus and/or bacteria and the free plants[22] and their constituents.[23,24] Furthermore, we performed that three *Rehmannia* species could be determined by DNA analysis.[25]

Green pharmacy becomes an impact trend in the pharmaceutical sciences, in which promotion of natural products is the key strategy.[26] As

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part of our ongoing study on utilization of nonsupplemented medicinal parts of principal medicinal plants such as *Bupleurum falcatum* Linne[27] and *Angelica acutiloba* (Siebold and Zucc.) Kitag.,[28] our present phytochemical investigation on the leaves of RG Liboschitz var. *purpurea* Makino led to the isolation of eight compounds including five triterpenes for the first time from RG. This article herein describes the isolation, structural identification, and documented pharmacological effects of these eight isolated compounds.

MATERIALS AND METHODS

General procedures

The procedures and equipment were employed in this research as follows: DIP-360 digital polarimeter (JASCO, Easton, USA) for recording optical rotations; JEOL ECX 400 FT-nuclear magnetic resonance (NMR) spectrometer (JEOL, Japan) and Bruker Avance 500 NMR spectrometer (Bruker BioSpin, Germany) for NMR measurement and operating at room temperature using standard pulse program, with tetramethylsilane as the internal standard and chemical shift values were expressed in δ (ppm); Agilent 1260 Triple Quad-6420LC-MS/MS (Agilent Technologies, USA) for ESI-MS experiment; the adsorbents including silica gel 60 (230–400 mesh, Nacalai Tesque Inc., Kyoto, Japan) and YMC ODS-A gel (50 µm, YMC Co. Ltd., Kyoto, Japan) for column chromatography; and finally, Kieselgel 60 F_{254} and Silica gel 60 RP-18 F_{254S} (Merck, Darmstadt, Germany) plates for thin-layer chromatography with the spraying reagent of 1% $Ce(SO_4)_2$-10% aqueous H_2SO_4 solution.

Plant materials

The leaves of the title plant were collected in Chiba University, Japan, in November 2018 and were taxonomically confirmed by one of the authors (YS). Voucher specimens (code RG201801) have been stored at the herbarium of Nagasaki International University, Japan.

Extraction and isolation

The leaf sample (150 g) after drying was pulverized and then extracted with 80% EtOH (400 mL × 3 times) at 40°C under sonication. The obtained residue (19.6 g) after removal of solvent was suspended in water (200 mL), followed by successively partitioning with *n*-hexane, EtOAc, and *n*-BuOH (each 200 mL × 3) to give portions of hexane (2.54 g), EtOAc (2.11 g), and BuOH (8.26 g), respectively.

The EtOAc portion (2.0 g) was loaded onto a silica gel column (250 g, Φ40 mm × 300 mm) with *n*-hexane-EtOAc (1000 mL, 5:1, v/v) to give six fractions (E1 ~ E6). The fraction E1 (180 mg) was then chromatographed on a reversed-phase C_{18} column (150 g, Φ20 mm × 350 mm) with MeOH-H_2O (600 mL, 5:1, v/v) and then sequenced by a silica gel column (150 g, Φ20 mm ×400 mm) with $CHCl_3$-EtOAc (500 mL, 20:1, v/v) to furnish 1 (11 mg). Next, the fraction E3 (230 mg) was chromatographed on a reversed-phase C_{18} column (150 g, Φ20 mm × 400 mm) with MeOH-H_2O (450 mL, 4:1, v/v) to yield compounds 2 (8 mg) and 3 (37 mg). Likewise, the fraction E5 (270 mg) was loaded onto a reversed-phase C_{18} column (150 g, Φ20 mm ×400 mm) with MeOH-H_2O (400 mL, 3:1, v/v) to obtain 4 (9 mg) and 5 (5 mg), respectively.

The BuOH residue (8.0 g) was subjected to a silica gel column (250 g, Φ40 mm × 300 mm) with a gradient of CH_2Cl_2-MeOH (1200 mL, 10:1→1:1, v/v) to give six fractions (B1 ~ B6). Fraction B3 (630 mg) was then chromatographed on a silica gel column with $CHCl_3$-MeOH-H_2O (600 mL, 5:1:0.1, v/v/v), followed by a RP column with MeOH-H_2O (500 mL, 3:2, v/v) to yield 8 (112 mg). Similarly, fraction B4 (580 mg) was loaded onto a silica gel column with $CHCl_3$-MeOH-H_2O (500 mL, 4:1:0.1, v/v/v), followed by a RP column with MeOH-H_2O (400 mL, 1:1, v/v) to yield 6 (21 mg). Subsequently, fraction B6 (750 mg) was chromatographed on a silica gel column with $CHCl_3$-MeOH-H_2O (600 mL, 7:3:0.4, v/v/v), followed by a RP column with MeOH-H_2O (400 mL, 3:4, v/v) to obtain 7 (31 mg).

RESULTS AND DISCUSSION

Previously, we confirmed that three *Rehmannia* species, RG, RG Liboschitz, and their hybrid, could be determined by DNA analysis[25] as it is suggested that there are many genetic diversities of RG.[29] Furthermore, we developed tissue and organ culture system of GL and isolated two iridoids, melittoside and rehmanioside D, a caffeoyl glycoside, acteoside, and ethyl-β-D-glucose in the regenerated shoots and leaves.[30] From this evidence and consistent with recent high-performance liquid chromatography quantitative analysis,[19] it is confirmed that iridoid and caffeoyl glycosides are the main hydrophilic constituents in the aerial part of RG. On the other hand, our chemical and chromatographic monitoring suggests the occurrence of terpenoids in the organic portion of the RG crude extract. Subsequently, various experiments in sequence of extraction, partition, and combined chromatographic techniques resulted in the separation of five ursane-type triterpenoids including ursolic acid (1),[31] pomolic acid (2),[32] 2β-hydroxypomolic acid (3),[32] asiatic acid (4),[33] and urs-12-ene-3 β,7β,24-triol-28-oic (5)[34] from the organic layer and three glycosides ajugol (6),[35] aucubin (8),[35] and acteoside (7)[36] from the polar portion of the crude ethanol extract of RG. Their structures, as shown in Figure 1, were identified based on the extensive spectroscopic data including NMR and MS spectra together with comparison with those in the literature.

Compound 5 was isolated as a white powder. ^1H and ^{13}C NMR spectra of 5 revealed features of an ursane-type triterpene.[31,32] The ^1H NMR spectrum revealed signals of an olefinic proton at δ 5.23 (1H, br s, H-12), two oxymethine protons (-CH-O-) at δ 3.76 (1H, br s, H-3α) and 3.90 (1H, dd, J = 11.6, 4.8 Hz, H-7α), two germinal protons of an oxymethylene function (–CH_2-O-) at δ 3.67 (1H, d, J = 11.6 Hz, H-24a) and 3.35 (1H, d, J = 11.6 Hz, H-24b), four tertiary methyl groups (δ 1.12 [3H, s, H-27], 1.09 [3H, s, H-23], 0.95 [3H, s, H-26], and 0.81 [3H, s, H-25]), and two secondary methyl groups (δ 0.94 [3H, d, J = 6.0 Hz, H-30] and 0.86 [3H,

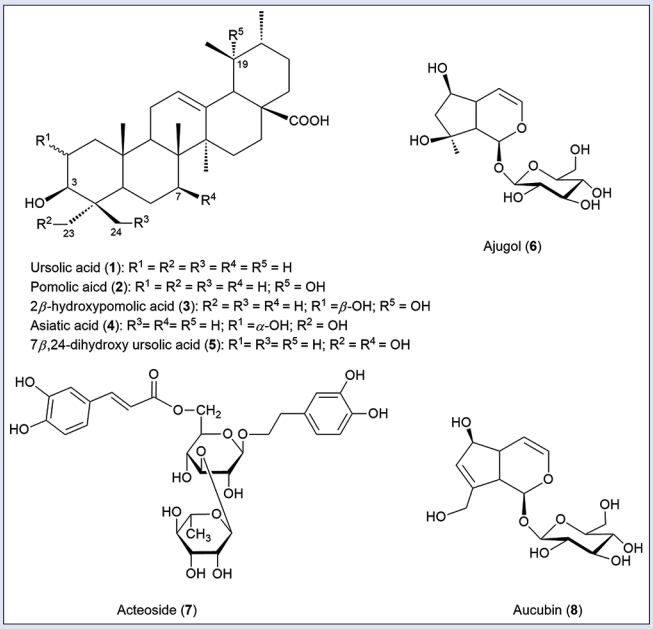

Figure 1: Structures of the eight isolated compounds from the *Rehmannia glutinosa* leaves

d, J = 6.0 Hz, H-29]), respectively. The ^{13}C NMR spectrum of 5 and DEPT exhibited thirty carbon signals of the ursane-type triterpene including a carboxylic carbon at δ 181.9 (C-28), two olefinic carbons at δ 126.7 (C-12) and 139.6 (C-13), two oxymethine carbons at δ 74.6 (C-3) and 67.1 (C-7), and an oxymethylene carbon at δ 65.9 (C-24). On the basis of the above analyses and comparison with respective reported data,[34] compound 5 was structurally elucidated as 7β,24-dihydroxy ursolic acid, which was first isolated from RG and *Rehmannia* spp.

Among the eight isolated compounds, besides the typical components of glycosides (iridoid and phenylethanoid skeletons), it is noteworthy that five ursane triterpenoids were first isolated from RG. There are only two minor triterpenoids in the up-to-date phytochemical database of the Rehmanniae Radix,[10] and recently, three unique ursane-type triterpenes were reported from its leaves.[20] So then, it supported that the organic extract of the RG leaves is rich in triterpenoids, which potentially constitute to discriminate chemical profiles between the RG aerial parts and the Rehmanniae Radix.

Triterpenoid is considered as the most universal and largest group of natural products in the plant kingdom and be found low toxicity in advantage and certain derivatives become lead compounds in drug development and clinically approved in the World.[31] To date, various pharmacological activities, such as antiosteoporosis, antiviral, antiprotozoal, anti-inflammatory, and antidiabetic activities, have been investigated for various triterpenes.[37-39]

Of these triterpenes, foremost, ursolic acid (1) represents various pharmacological benefits including anticancer, antimicrobial, anti-inflammation, antiobesity, antiatherosclerosis, hepatoprotection, antianxiety, antidepression and antiosteoporosis, and other pharmacological effects.[40] Pomolic acid (2) is known as the main active component of *Euscaphis japonica* and exerts potential anticancereous, anti-inflammatory, and antidiabetic activities.[41] In addition, asiatic acid (4) is originally isolated from and as a prominent triterpenoid of *Centella asiatica*, which possesses a wide spectrum of biological effects, notably, of anticancer, anti-inflammation, antidiabetes, antioxidant and hepatoprotection, anti-hepatitis C virus, and neuroprotection, respectively.[42] In this regard, our previous bioassay-guided investigation revealed several ursane triterpenoids including ursolic acid and asiatic acid from *Eriobotrya japonica*[43] and *Salvia miltiorrhiza*[44] as active components with antiproliferation[44] and antiobesity through inhibitory effects on ghrelin production,[43] respectively.

CONCLUSION

Our study clarified that the EtOAc extract prepared from the RG leaves contained various triterpenes. Although we qualitatively determined the concentration of iridoid glycosides such as catalpol, rehmanniosides A–D, leonuride, and aucubin in the RG root,[22] it was suggested that the aerial part of RG contains a lower concentration of iridoid glycosides.[30] Taken together, since the triterpenoid content is of not low yield and should be concentrated in EtOAc extract, especially along with potential of unique components, it becomes evident that triterpenoid components should be notable in addition to well-documented hydrophilic glycosides in the chemical profile of the RG leaves and need to be more explored. Consequently, the investigation of various ursane-type triterpenoids in the RG leaves contributed partly to phytochemical database and evidence of the pharmacological benefit associated with its potential in medicinal use.

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Conflicts of interest

There are no conflicts of interest.

Supplementary Information

Supporting data accompanies this article available on the internet at http://www.phcog.com/.

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