Four New Acyclic Diterpenes From *Siegesbeckia orientalis*

Do Thi Trang¹, Phan Thi Thanh Huong¹, Nguyen Thi Cuc¹, Duong Thi Dung¹, Bui Thi Thu Trang², Nguyen Xuan Nhiem¹,³, Bui Huu Tai¹,³, and Phan Van Kiem¹,³

Abstract

Four new acyclic diterpenes, siegetalis A-D (1-4), were isolated from the aerial parts of *Siegesbeckia orientalis*. Their chemical structures were elucidated by extensive analysis of high-resolution electrospray ionization mass spectrometry and nuclear magnetic resonance spectral data. The effects of the isolated compounds on the activity of xanthine oxidase were evaluated by the oxidative reaction with xanthine as a substrate. At a concentration of 50 µM, compounds 1-4 exhibited xanthine oxidase inhibitory activity at levels of 13.59% ± 0.51%, 19.64% ± 1.54%, 17.45% ± 1.26%, and 21.36% ± 1.40%, respectively.

Keywords

compositae, *Siegesbeckia orientalis*, acyclic diterpene, siegetalis, xanthine oxidase activity

Received: September 18th, 2021; Accepted: October 11th, 2021.

Introduction

The *Siegesbeckia* genus (Compositae family) comprises about 20 species worldwide. They are distributed in the tropical, subtropical, and temperate areas of the world and mainly found in Central China, Northern Vietnam, and other South-East Asian countries.¹,² Three *Siegesbeckia* species have been popularly used as traditional medicines, *S. orientalis*, *S. glabrescens*, and *S. pubescens*.³ Phytochemical study of the *Siegesbeckia* genus has, therefore, mostly focused on those three species. Up to date, over 250 compounds have been identified and divided into three main groups, sesquiterpenoids (germacrane, guaiane, and cadinene types), diterpenoids (kaurane and pimarane types), and phenolics (flavone, flavanone, isoflavone, and chalcone).⁴⁻⁸ The secondary metabolites from *Siegesbeckia* species have been reported having antioxidative, antiallergic, fertility, anti-inflammatory, and cytotoxic activities.⁶⁻⁹ *S. orientalis* L is an annual herb. Its aerial parts are commonly used in traditional Chinese medicine to treat hypertension, rheumatic arthritis, malaria, and neurasthenia, along with other topical injuries.¹⁰ In traditional Vietnamese medicine, the aerial parts of *S. orientalis* have been additionally used to treat gout and reducing pain.³ Our previous study revealed benzoate esters from the aerial part of *S. orientalis* as potential xanthine oxidase inhibitors.¹¹ Continuing our study of the chemical constituents of *S. orientalis* and their role in the treatment of gout, herein, we describe the identification of four new acyclic diterpenes from *S. orientalis* (Figure 1). Their effects on the activity of xanthine oxidase were evaluated by the oxidative reaction with xanthine as substrate.

Results and Discussion

The aerial parts of *S. orientalis* was ultrasonically extracted with methanol. The crude extract was fractionated by open column chromatography and later purified by semipreparative high-performance liquid chromatography (HPLC) to give compounds 1-4.

Compound 1 was obtained as a white amorphous powder. Its molecular formula was determined to be C₂₀H₃₄O₄ by the quasimolecular ion peaks at m/z 373.2138 [M+35Cl]− and m/z 375.2127 [M+37Cl]− (calculated for C₂₀H₃₄O₄Cl, 373.2146 and 375.2116) in the high-resolution electron spray ionization mass spectrum (HRESIMS), indicating four degrees of unsaturation.
(1H NMR) and heteronuclear single quantum coherence (HSQC) spectra of 1 showed signals assigning to four olefinic protons ($\delta^1_H$ 5.53 [1H, $t$, $J = 7.0$ Hz], 5.45 [1H, $t$, $J = 7.0$ Hz], 5.33 [1H, $t$, $J = 7.0$ Hz], and 5.09 [1H, $t$, $J = 7.0$ Hz]), three oxygenated methylene groups ($\delta^1_H$ 4.22 [2H, s], 4.08 [2H, s], and 4.06 [2H, $d$, $J = 7.0$ Hz]), an oxygenated methine group ($\delta^1_H$ 4.13 [1H, $dd$, $J = 6.5$ and 6.0 Hz]), and three singlet methyl groups ($\delta^1_H$ 1.75, 1.72, and 1.63 [each 3H, s]). The $^{13}$C NMR and HSQC spectra of 1 revealed signals for 20 carbon atoms, including eight olefinic carbons (four quaternary and four tertiary), four oxygenated carbons (three methylenes and one methine), and eight aliphatic carbons (five methylenes and three methyl groups). The presence of four double bonds and four degrees of unsaturation indicated 1 to be an acyclic diterpene. Moreover, the NMR data of 1 were similar to those of 18-acetoxy-12,19-dihydroxy geranyl nerol (1a), except for the lack of signals for the acetyl group. The structure of 1 was further demonstrated by H-H correlation spectroscopy and heteronuclear multiple bond correlation (HMBC) correlations, as shown in Figure 2. The HMBC correlations between $H_2-1$ ($\delta^1_H$ 4.06)/$H_1-20$ ($\delta^1_H$ 1.75) and C-2 ($\delta^C$ 124.7)/ C-3 ($\delta^C$ 139.5) confirmed the locations of a hydroxy group at C-1 and

![Figure 1. Chemical structures of compounds 1 to 4 isolated from Siegesbeckia orientalis.](image1)

![Figure 2. Important HMBC correlations of 1 to 4 and COSY correlations of 1 and 2. Abbreviations: COSY, correlation spectroscopy; HMBC, heteronuclear multiple bond correlation.](image2)
a double bond at C-2/C-3. The HMBC correlations between H2-19 (δH 4.08) and C-6 (δC 128.7)/C-7 (δC 138.4)/C-8 (δC 35.6) confirmed the locations of a hydroxy group at C-19 and a double bond at C-6/C-7. The HMBC correlations between H2-18 (δH 4.22) and C-10 (δC 130.8)/C-11 (δC 139.5)/C-12 (δC 76.7) confirmed the location of a hydroxy group at C-18, C-12 and a double bond at C-10/C-11. Later, the HMBC correlations between H1-16 (δH 1.63)/H2-17 (δH 1.72) and C-14 (δC 120.1)/C-15 (δC 134.8) confirmed the double bond at C-14/C-15. The geometric configuration of the double bonds at C-2/C-3 and C-6/C-7 were determined to be 2Z and 6Z by δC values of C-20 (δC 23.5) and C-19 (δC 60.0), respectively, in comparison with the previous reports (2Z: δC = 23.4, 2E: δC = 16.3, 6Z: δC = 60.1, 6E: δC = 67.0). The geometric pattern of the double bond at C-10/C-11 was deduced to be similar to that of the double bond at C-6/C-7 by the δC value of C-18 (δC 57.9). However, according to the priority of substituted groups at C-11, the geometric configuration of the double bond at C-10/C-11 was then determined to be 10E. Consequently, compound 1 was determined to be 12,18,19-trihydroxygeranylnerol, (1,12,18,19-tetrahydroxyphyta-2Z,6Z,10E,14-tetraene) and named siegetalis A (Figure 1 and Supplemental Figures S1-S9).

Compound 2 was obtained as a white amorphous powder. Its molecular formula was determined to be C22H38O7 by the quasimolecular ion peaks at m/z 449.2302 [M + Cl]− and m/z 451.2292 [M + Cl]− (calcd. for C22H38O7Cl, 449.2306 and 451.2277) in the HRESIMS (Supplemental Figures S10 and S11), indicating four degrees of unsaturation. As shown in Table 1, the 1H and 13C NMR data of 2 are partially identical to those of 1, indicating that they shared the same structural fragment from C-1 to C-9. The appearance of additional signals corresponding to carbonyl (δC 171.3) and methyl groups (δC 21.1 and δC 2.06) indicated the presence of an acetoxy group in 2. The HMBC correlations between H2-18 (δH 4.72 and 4.65) and C-1′ (δC 171.3)/C-10 (δC 133.3)/C-11 (δC 136.3)/C-12 (δC 75.5) demonstrated the location of the acetoxy group at C-18 and a hydroxy group at C-12. On the other hand, HMBC correlations between H2-16 (δH 1.17)/H3-17 (δH 1.21) and C-14 (δC 78.5)/C-15 (δC 72.6) indicated the presence of hydroxy groups at C-14 and C-15. Thus, the structure of 2 was determined to be 18-acetoxy-1,12,14,15,19-pentahydroxyphyta-22Z,6Z,10E-triene, and named siegetalis B (Figure 1 and Supplemental Figures S10-S18).

Compound 3 was obtained as a white amorphous powder. Its molecular formula was determined to be C20H34O5 by quasimolecular ion peaks at m/z 389.2089 [M + Cl]− and m/z 389.2075 [M + Cl]− (calcd. for C20H34O5Cl, 389.2095 and 391.2065) in the HRESIMS (Supplemental Figures S19 and S20), indicating four degrees of unsaturation. Like 1 and 2, the 1H and 13C NMR data of 3 were partially identical to those of 1 and 2 (Table 1, Supplemental Figures S21-S26).

### Table 1. 1H NMR and 13C NMR Spectroscopic Data for Compounds 1 to 4.

| No. | 1 (CDCl3) | 2 (CDCl3) | 3 (CDCl3) | 4 (CD3OD) |
|-----|-----------|-----------|-----------|-----------|
|     | δC (δH) | δC (δH) | δC (δH) | δC (δH) |
| 1   | 58.7     | 4.06 (d, 7.0) | 58.8     | 4.07 (d, 7.0) |
| 2   | 124.7    | 5.45 (t, 7.0) | 124.8    | 5.47 (t, 7.0) |
| 3   | 139.5    | -          | 139.5    | -          |
| 4   | 32.1     | 2.14 (m)/2.18 (m) | 32.0     | 2.14 (m)/2.18 (m) |
| 5   | 26.2     | 2.18 (m)/2.21 (m) | 26.3     | 2.18 (m)/2.21 (m) |
| 6   | 128.7    | 5.33 (t, 7.0) | 128.3    | 5.32 (t, 7.0) |
| 7   | 138.4    | -          | 138.4    | -          |
| 8   | 35.6     | 2.20 (m) | 34.8     | 2.21 (m) |
| 9   | 26.3     | 2.25 (m)/2.35 (m) | 25.9     | 2.31 (m) |
| 10  | 130.8    | 5.53 (t, 7.0) | 133.3    | 5.79 (t, 7.0) |
| 11  | 139.5    | -          | 136.3    | -          |
| 12  | 76.7     | 4.13 (dd, 6.5, 6.0) | 75.5     | 4.37 (dd, 9.0, 3.0) |
| 13  | 34.9     | 2.24 (m) | 36.7     | 1.62 (m) |
| 14  | 120.1    | 5.09 (t, 7.0) | 78.5     | 3.61 (dd, 10.0, 2.0) |
| 15  | 134.8    | -          | 72.6     | -          |
| 16  | 18.1     | 1.63 (s) | 24.0     | 1.17 (s) |
| 17  | 25.9     | 1.72 (s) | 26.2     | 1.21 (s) |
| 18  | 57.9     | 4.22 (s) | 59.7     | 4.65 (dd, 12.5) |
| 19  | 60.0     | 4.08 (s) | 60.0     | 4.10 (s) |
| 20  | 23.5     | 1.75 (s) | 23.4     | 1.75 (s) |
| 1′  | 171.3    | -          |         | -          |
| 2′  | 21.1     | 2.06 (s) | 20.9     | 2.05 (s) |
indicating that compounds 1-3 shared the same structural fragment from C1 to C-9. Furthermore, the similar pattern of HMBC correlations between 2 and 3 (Figure 2) demonstrated additional oxygenated carbons at C-12, C-14 and C-15. Although the HMBC spectrum did not clearly show a correlation between H-12 (δ H 4.51) and C-15 (δ C 84.2), the downfield movement of δ C 12 (δ C 80.4) and δ C 15 (δ C 84.2) in comparison with those of 2 (δ C 12 75.5 and δ C 15 72.6) suggested the presence of an epoxide bridge between C-12 and C-15. This deduction was consistent with a molecular formula of C22H38O7, obtained by HRESIMS analysis. The relative configuration between C-12 and C-14 was proposed to be cis by comparison of the δ C 12 value (80.7) with those of previous reports (cis [3a]: δ C 12 80.7 and trans [3b]: δ C 12 82.2) (Supplemental Figure 36).15 Because the difference between 80.7 for cis and 82.2 for trans in the literature is small, the substituent is slightly different from that of 3, and the nuclear Overhauser effect spectroscopy and rotating-frame nuclear Overhauser effect correlation spectroscopy (ROESY) spectra did not give enough data for the relative configuration to be established of the 4′-hydroxy-5,5′-dimethylenetetrahydrofuranyl group,15 the relative configuration of 3 is still undetermined. Consequently, compound 3 was determined to be 12,15-epoxy-1,14,18,19-tetrahydroxy-2Z,6Z,10E-triene, and named siegetalis C.

Compound 4 was obtained as a white amorphous powder. HRESIMS analysis of 4 showed quasimolecular ion peaks at m/z 449.2300 [M + 35Cl]− and m/z 451.2272 [M + 37Cl]−, which indicated its molecular formula to be C22H38O7, an isomer of 2 (Supplemental Figures S27 and S28). Different to 2, however (Supplemental Figures S29 and S34) were the HMBC correlations between H3-16 (δ H 1.64)/H3-17 (δ H 1.72) and C-14 (δ C 121.8)/C-15 (δ C 134.1), which indicated the presence of a double bond at C-14/C-15, and the HMBC correlations between H5-20 (δ H 1.17)/H5-21 (δ H 3.75 and 3.55) and C-2 (δ C 78.5)/C-3 (δ C 74.8), which indicated the presence of hydroxy groups at C-2 and C-3. Thus, compound 4 was determined to be 18-acetoxy-1,2,3,12,19-pentahydroxyphytya-6Z,10E,14-triene, and named siegetalis D. The absolute configurations of the secondary hydroxy groups in compounds 1-4 were attempted using a modified Mosher’s method.16 Compounds 1-4 contain, in total, four secondary and primary hydroxy groups in each molecule. Unfortunately, the desired Mosher’s ester products of the secondary hydroxy groups were not successfully obtained among the reaction products. Therefore, the absolute configurations of the secondary hydroxy group in compounds 1-4 are undetermined.

Acyclic diterpenes are basic diterpenoids and structurally characterized by dimerization of geranyl and/or neryl groups. Their main backbone is a linear C16 with four double bonds bearing six olefinic methyl groups. A huge diversity of substitutions such as oxygenation at the terminal methyl groups, different patterns of unsaturation, formation of an epoxy ring, and geometric isomerization of double bonds leads to high stereochemical diversity of acyclic diterpenes. Acyclic diterpenes were reported to be the largest natural product class from lipophilic extracts of seaweed, with numerous biological activities, such as antimicrobial, anti-inflammatory, neuroprotective, antitubercular, and anticancer. A few geranylnerol-type acyclic diterpenes have been previously isolated from S orientalis.18

The raw materials of S orientalis have been used in traditional medicines to treat gout. Thus, compounds 1-4 were evaluated for their effect on xanthine oxidase activity, an important enzyme causing gout. The assay was carried out based on the oxidative reaction of xanthine to uric acid in the presence of xanthine oxidase as a catalyst. At a concentration of 50 µM, compounds 1-4 weakly inhibited xanthine oxidase activity with inhibitory percentages of 13.59% ± 0.51%, 19.64% ± 1.54%, 17.45% ± 1.26%, and 21.36% ± 1.40%. Allopurinol (6.25 µM) was used as a positive control with an inhibitory rate of 80.2% ± 4.8%.

**Material and Methods**

**General Experimental Procedures**

Optical rotation was measured on a Jasco P-2000 polarimeter, HRESIMS on an Agilent 6530 Accurate Mass Quadrupole Time of Flight (Q-TOF) system, and NMR spectra on a Bruker Avance III 500 MHz spectrometer. Preparative HPLC was acquired on an Agilent 1260 Infinity II system equipped with a YMC J’sphere ODS-H80 (20 × 250 mm, 4 µm) HPLC column. Flash column chromatography was performed using either silica gel or reversed phase (RP-18) resins as adsorbent. Thin layer chromatography was carried out on precoated silica gel 60 F254 and/or RP-18 F254S Plates.

**Plant Material**

The plant samples were collected at Hoa Binh province in February 2020. The scientific name of the plant was determined to be S orientalis L. (Compositae) by Dr Nguyen The Cuong (Institute of Ecology and Biological Resources, VAST). A voucher specimen (code: NCCT-P88) is kept at the Institute of Marine Biochemistry, VAST.

**Extraction and Isolation**

Aerial parts of S orientalis were air dried and pulverized into fine powder. The sample material (9 kg) was extracted with methanol in an ultrasonic bath, three times (20 L of methanol and 60 min at room temperature each time). After removal of the solvent *in vacuo*, the dark residue (250 g) was suspended in water and successively extracted with dichloromethane and ethyl acetate (EtOAc). The EtOAc extract was roughly fractionated by silica gel column chromatography using a gradient solvent system of dichloromethane/methanol (40/1→0/1, v/v) to obtain four fractions, E1-E4. Fraction E1 was continuously separated on a RP-18 column eluting with methanol/water (2/1, v/v) to obtain three subfractions, E1.1-E1.3. Subfraction E1.2 was...
purified by preparative HPLC with acetonitrile (ACN)/water (25/75, v/v) to give compound 2 (12.0 mg, tR 32.3). Sub-fraction E1.3 was purified by preparative HPLC using ACN/water (45/55, v/v) to give compound 1 (10.0 mg, tR 29.1). Fraction E2 was first chromatographed on a silica gel column with dichloromethane/acetone (3/1, v/v) and then further purified by preparative HPLC using ACN/water (25/75, v/v) to yield compound 3 (9.0 mg, tR 47.6). Fraction E4 was subjected to silica gel chromatography eluting with dichloromethane/acetone (3/1, v/v) and then further purified by preparative HPLC using ACN/water (30/70, v/v) to yield compound 4 (20 mg, tR 55.4).

Siegetalis A (1). White amorphous powder, $[\alpha]_D^{25}$ -44.1 (c 0.1, MeOH); infrared spectrum (IR) (KBr): $\nu_{\max}$ 3404, 2956, 2890, 1622 cm$^{-1}$; HRESIMS $m/z$ 373.2138 [M + 35Cl]$^-$ and $m/z$ 375.2127 [M + 37Cl]$^-$ (calculated for C22H38O7Cl, 373.2146 and 375.2116); $^1$H NMR (CDCl$_3$, 500 MHz) and $^{13}$C NMR (CDCl$_3$, 125 MHz) data are given in Table 1.

Siegetalis B (2). White amorphous powder, $[\alpha]_D^{25}$ +31.5 (c 0.1, MeOH); IR (KBr): $\nu_{\max}$ 3410, 2970, 2892, 1705, 1628, 1180 cm$^{-1}$; HRESIMS $m/z$ 449.2302 [M + 35Cl]$^-$ and $m/z$ 451.2292 [M + 37Cl]$^-$ (calcd. for C22H38O4Cl, 449.2306 and 451.2277); $^1$H NMR (CDCl$_3$, 500 MHz) and $^{13}$C NMR (CDCl$_3$, 125 MHz) data are given in Table 1.

Siegetalis C (3). White amorphous powder, $[\alpha]_D^{25}$ +54.0 (c 0.1, MeOH); IR (KBr): $\nu_{\max}$ 3400, 2968, 2883, 1624, 1184 cm$^{-1}$; HRESIMS $m/z$ 389.2089 [M + 35Cl]$^-$ and $m/z$ 391.2075 [M + 37Cl]$^-$ (calcd. for C20H34O5Cl, 389.2095 and 391.2065); $^1$H NMR (CDCl$_3$, 500 MHz) and $^{13}$C NMR (CDCl$_3$, 125 MHz) data are given in Table 1.

Siegetalis D (4). White amorphous powder, $[\alpha]_D^{25}$ -62.7 (c 0.1, MeOH); IR (KBr): $\nu_{\max}$ 3406, 2988, 1708, 1618, 1192 cm$^{-1}$; HRESIMS $m/z$ 449.2300 [M + 35Cl]$^-$ and $m/z$ 451.2272 [M + 37Cl]$^-$ (calcd. for C22H38O5Cl, 449.2306 and 451.2277); $^1$H NMR [CD$_3$OD, 500 MHz] and $^{13}$C NMR [CD$_3$OD, 125 MHz] data are given in Table 1.

Xanthine Oxidase Assay

Compounds 1-4 and allopurinol were dissolved in dimethyl sulfoxide at a concentration of 10 mM and diluted with buffer to the required concentrations. The xanthine oxidase activity assay was performed using xanthine as the substrate, as previously described. In brief, 100 µL solution of xanthine oxidase (0.03 U/mL) in phosphate buffer (50 mM, pH 7.5) was mixed with 50 µL solution of samples (200 µM) in a 96-well plate. The plate was incubated for 5 min at 37°C and then the reaction was initiated by adding 50 µL of a solution of xanthine (0.60 mM) to each well. The absorbance of the reaction mixture at 295 nm was recorded every minute for 10 consecutive minutes by microplate reader (Infiniti 200Pro, Tecan Group Ltd). For comparison, 50 µL of buffer solution and allopurinol (25 µM) were used as a vehicle and positive control, respectively. The xanthine oxidase inhibitory activity was deduced by the difference in absorbance between samples and vehicle wells $[(A_{\text{vehicle}} - A_{\text{sample}})/A_{\text{vehicle}}]$. 

Conclusions

Phytochemical study of the aerial parts of S orientalis revealed four new acyclic diterpenes, 1,12,18,19-tetrahydroxyphytadiene-2Z,6Z,10E-triene (siegetalis A, 1), 18-acetoxy-1,12,14,15,19-pentahydroxyphytadiene-2Z,6Z,10E-triene (siegetalis B, 2), 12,15-epoxy-1,14,18,19-tetrahydroxyphytadiene-2Z,6Z,10E-triene (siegetalis C, 3), and 18-acetoxy-1,2,3,12,19-pentahydroxy phytadiene-6Z,10E,14-triene (siegetalis D, 4). At a concentration of 50 µM, compounds 1-4 exhibited weak xanthine oxidase inhibitory activity with inhibitory rates in the range of 13.59% ± 0.51% to 21.36% ± 1.40%.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Vietnam Academy of Science and Technology (grant number DLTE00.07/20-21).

Author Contributions

BH Tai and PV Kiem contributed to research idea; DT Trang, PTT Huong, NT Cu, DT Dung contributed to isolation; BH Tai, BTT Trang, NX Nhiem, PV Kiem contributed to structure elucidation and writing.

Ethical Approval

Our institution does not require ethical approval for reporting individual cases or case series.

ORCID iD

Phan Van Kiem https://orcid.org/0000-0003-0756-6990

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

Trial Registration

Not applicable, because this article does not contain any clinical trials.
Supplemental Material

Supplemental material for this article is available online.

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