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New sesquiterpene derivatives from stems and leaves of *Smallanthus sonchifolius*

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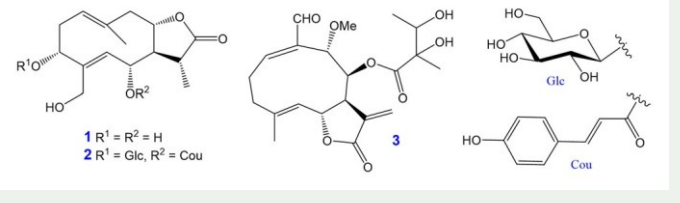
ABSTRACT

From the MeOH residue of *Smallanthus sonchifolius* stems and leaves, three new sesquiterpene derivatives, namely smallantholides A – C (**1** – **3**), and two know phenyl propanoid glycosides (**4** and **5**), were isolated using various chromatographic techniques. The structural elucidation was confirmed by spectroscopic methods including 1D, 2D NMR, CD and HR-TOF-MS. Moreover, the *in vitro* α-glucosidase inhibitory activity of **1** – **5** was also evaluated.



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1. Introduction

Yacon, a long-lived herbaceous plant indigenous to the Andean zone, is attracting global interest due to its prebiotic benefits and overall health advantages. The tuberous roots are commonly employed as natural syrups and sweeteners to address digestive issues, especially in terms of maintaining intestinal microbiota balance. Moreover, the traditional Andean people associate the dried yacon leaves with anti-diabetic properties, using them in teas as a component of low-calorie diets (Delgado et al. 2013). In Vietnam, this plant was introduced and cultivated in Sapa, Lao Cai, starting in 2000 (Thu et al. 2019). It has been published to exhibit a range of bioactive effects, such as antidiabetic, antimicrobial, hypoglycaemic, antioxidant, and hepatoprotective properties (Lock et al. 2016). Previous investigations have identified the principal components of this plant as sesquiterpene lactones (Lin et al.

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2003; Hong et al. 2008; Frank et al. 2013; De Ford et al. 2015; Kitai et al. 2015; Yuan et al. 2017; Ran et al. 2018) and diterpene derivatives (Mercado et al. 2010; Lock et al. 2016). In our recent research on the chemical compounds of Vietnamese medicinal plants concerning their α-glucosidase inhibitory effects (Hanh et al. 2024), the current study focuses on the separation and structural characterisation of three new sesquiterpene derivatives and two known phenylpropanoid glycosides from the stems and leaves of *Smallanthus sonchifolius*. Their α-glucosidase inhibition was also estimated.

2. Results and discussion

An exploration of phytochemicals of *Smallanthus sonchifolius* stems and leaves afforded three new sesquiterpene derivatives (**1** – **3**, Figure 1) and two known phenyl propanoid glycosides. The known compounds, dictamnoside A (**4**) (Miyase et al. 1985) and eugenyl-*β*-D-glucopyranoside (**5**) (Chassagne et al. 1997), were identified through comprehensive analysis of the 2D and 1D NMR data compared with reported evidence.

Smallantholide A (**1**) was obtained in the form of a non-crystalline powdered substance with the constitutional formula $C_{15}H_{22}O_5$, identified by HR-TOF-MS with an ion signal at *m/z* 283.1536 $[M + H]^+$. The proton NMR spectrum revealed signals for two olefinic protons [δ_H 5.21 (br d, *J* = 11.4 Hz, H-1) and 5.34 (br d, *J* = 10.2 Hz, H-5)], three oxymethines [δ_H 4.69 (br s, H-3), 4.46 (br t, *J* = 9.6 Hz, H-6), 4.19 (dd, *J* = 9.0, 9.6 Hz, H-8)], one oxymethylene [δ_H 3.72 and 4.26 (each d, *J* = 12.6 Hz, H_2-15)], one doublet methyl [δ_H 1.41 (d, *J* = 7.2 Hz, H_3-13)], and one singlet methyl [δ_H 1.49 (s, H_3-14)]. Furthermore, fifteen carbon peaks were detected in the carbon NMR experiment, suggesting it is a sesquiterpene derivative. This spectrum further supported the existence of two tri-substituted C = C bonds [δ_C 127.5 (C-1)/δ_C 133.8 (C-10) and δ_C 140.9 (C-4)/δ_C 133.4 (CH, C-5)], three oxymethines [δ_C 71.6 (C-3), 70.3 (C-6), and 81.4 (C-8)], one oxymethylene [δ_C 59.3 (C-15)], two methyl groups [δ_C 18.0 (C-13)

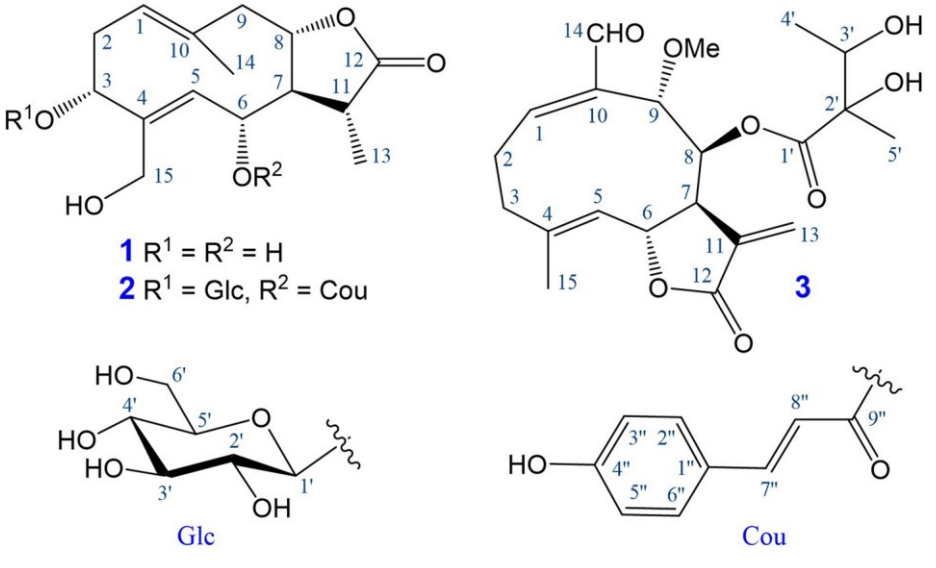

Figure 1. structures of **1** – **3**.

and 16.9 (C-14)], and one lactone carbonyl carbon [δ_C 181.6 (C-12)]. The data above are similar to those of 11*β*H-dihydrochamissonin (see Table S1) (Herz and Kumar 1981), except for the occurrence of the oxymethylene in **1**, which replaces one methyl in 11*β*H-dihydrochamissonin. Comprehensive examination of the ^{1}H-^{1}H COSY and HMBC interactions (Figure S22) established the plain structure of **1**. The HMBC interactions of proton H-15 with carbons C-5, C-4, and C-3 obviously confirm the location of the C-15 oxygenated methylene. The small *J* value between H-3 and H-2 (H-3 revealed a broad singlet signal) supported the *α*-orientation of the 3-OH group. The large *J* values between H-7 and H-6 (*J* = 9.6 Hz), H-7 and H-11 (*J* = 9.6 Hz), and H-7 and H-8 (*J* = 9.0 Hz) supported the *β*-orientation of H-11, H-8 and H-6, and the *α*-orientation of H-7 (Herz and Kumar 1981; Gershenzon et al. 1984). In addition, H-7 revealed a NOE correlation with H-13 but exhibited no interactions with H-6 and H-8; a NOE interaction of H-11 with H-6 further confirmed the spatial structure at C-11, C-8, C-7, and C-6.

Smallantholide B (**2**) was likewise received as an amorphous powder. Its ^{13}C and ^{1}H NMR spectral data closely resembled those of **1**, apart from the additional existence of peaks for a *β*-D-glucopyranosyl group [δ_C 102.7 (C-1′), 78.1 (C-5′), 78.0 (C-3′), 75.3 (C-2′), 71.7 (C-4′), and 62.8 (C-6′)/δ_H 4.46 (H-1′, d, *J* = 7.8 Hz)] and a (*E*)-*p*-coumaroyl functional group [δ_C 168.2 (C-9′′), 161.5 (C-4′′), 147.3 (C-7′′), 131.3 (C-6′′ and C-2′′), 127.0 (C-1′′), 116.9 (C-5′′ and C-3′′), and 114.9 (C-8′′)/δ_H 7.66 (H-7′′, d, *J* = 16.2 Hz), 7.48 (H-6′′ and H-2′′, d, *J* = 8.4 Hz), 6.83 (H-5′′ and H-3′′, d, *J* = 8.4 Hz), and 6.32 (H-8′′, d, *J* = 16.2 Hz)] (Van et al. 2020). This was additionally endorsed by HR-TOF-MS, which showed an ion signal at *m/z* 613.2228 $[M + Na]^+$. The H-1′ anomeric proton showed one HMBC interaction with C-3, indicating the glycosylation of the glucose at C-3. The esterification position of the coumaroyl group at C-6 was pinpointed by an HMBC interaction of H-6 with C-9′′ (Figure S22).

The ^{13}C and ^{1}H NMR spectral data of mallantholide C (**3**) are also indicative of a sesquiterpene derivative that has typical signals of two trisubstituted double bonds [δ_C 159.9 (C-1) and 141.5 (C-10)/δ_H 7.00 (H-1, dd, *J* = 10.2, 7.8 Hz) and δ_C 139.2 (C-4) and 128.2 (C-5)/δ_H 5.03 (H-5, br d, *J* = 10.8 Hz)], one 1,1-disubstituted double bond [δ_C 136.2 (C-11) and 122.2 (C-13)/δ_H 5.78 and 6.16 (H-13, each signal: d, *J* = 3.0 Hz)], three oxymethines [δ_C 79.7 (C-9), 76.9 (C-6), and 72.6 (C-8)/δ_H 6.58 (H-8, dd, *J* = 1.8, 8.4 Hz), 5.18 (H-6, t, *J* = 10.2 Hz), and 3.62 (H-9, dd, *J* = 8.4, 1.8 Hz)], one lactone carbonyl [δ_C 171.5 (C-12)], one aldehyde [δ_C 196.5 (C-14)/δ_H 9.44 (H-14, d, *J* = 2.4 Hz)], and one methyl [δ_C 17.1 (C-15)/δ_H 1.99 (H-15, d, *J* = 1.2 Hz)]. These data (Table S1) were comparable to those of 8*β*-epoxyangeloyloxy-9*α*-ethoxy-14-oxo-acanthospermolide (Hong et al. 2008), except for the significant difference in their substituents. The ^{13}C and ^{1}H NMR spectra clearly confirmed the existence of one methoxy group [δ_C 56.9 (C-1′′)/δ_H 3.14 (H-1′′, s)] and a 2′,3′-dihydroxy-2′-methylbutanoxyl moiety [δ_C 174.4 (C-1′), 78.7 (C-2′), 62.9 (C-3′), 23.9 (C-5′), and 18.8 (C-4′)/δ_H 4.34 (H-3′, q, *J* = 6.6 Hz), 1.52 (H-4′, d, *J* = 6.6 Hz), and 1.44 (H-5′, s)] (Yang et al. 2004). This was also established by HR-TOF-MS with the observation of an ion signal at *m/z* 408.2018 $[M - H_2O + NH_4]^+$. Detailed assessment of the COSY and HMBC interactions of **3** unambiguously confirmed its planar structure (Figure S22). The HMBC interactions of C-1′ with H-8 and that of C-1′′ with H-9 indicated relevant attachments of the 2′,3′-dihydroxy-2′-methylbutanoxyl and methoxy moieties at positions C-8 and C-9. In NOESY experiment, the interactions of H-14 with H-1 and

H-15 with H-6 indicated an *E* configuration for both C-4/C-5 and C-1/C-10 C = C bonds. The H-8/H-9 coupling constant (*J* = 8.4 Hz) is consistent with the α-orientation of H-8 (Hong et al. 2008). The NOESY relationships of H_α-8 with H_α-7 and H-13 and those of H_β-9 with H-15 and H_β-2 supported the alpha configuration of H-8 and H-7 as well as the β-orientation of H-9. In addition, the configuration of **3** was further verified by the CD spectrum with a strong negative Cotton effect at 224 nm (Hong et al. 2008).

The α-glucosidase inhibitory activity of compounds **1** − **5** were assessed using formerly reported method with slight modifications (Bharadwaj et al. 2018; Hanh et al. 2024). However, no compounds showed inhibitory effect at concentrations up to 200 µM.

3. Experimental

3.1. Plant material

The *Smallanthus sonchifolius* (Poepp. & Endl.) H. Robinson stems and leaves were collected at Bat Xat, Lao Cai, Vietnam, in May 2024. The exact species was distinguished by the author Dr. Nguyen The Cuong. Voucher specimens (No: SS.5.2024) were kept at the Institute of Biology, VAST, Hanoi capital, Vietnam.

3.2. Extraction and isolation

The stems and leaves (dried in air) of *S. sonchifolius* (3.5 kg) were cut, ground into powder and performed three sequential extractions using CH_3OH in ultrasonic equipment (1 h each time). The obtained solutions were paper filtered, merged and evaporated under evacuated conditions to yield a CH_3OH crude precipitate (M, 600 g). This was dissolved in H_2O (3 l) and sequentially extracted with *n*-hexane, CH_2Cl_2, and EtOAc furnishing the corresponding residues: *n*-hexane (H, 350 g), CH_2Cl_2 (D, 20.0 g), EtOAc (E, 1.0 g) and water part (W, 3 l). The aqueous portion was separated into three fractions W1-W3 employing Diaion HP-20 column with step-wise solvent system of CH_3OH − H_2O (0:100, 25:75, 75:25 and 100:0, v/v) and the removal of water eluted solution. Based on TLC behaviour, extract E (1 g) and fraction W3 (17 g) were merged and isolated on RP-18 MPLC with gradient CH_3OH − H_2O eluent (1:4→4:1, v/v) to yield seven fractions, W3A-W3G. Fractions W3D and W3E were merged and further isolated into five fractions (W3D1-W3D5) employing silica gel column with eluent of CH_2Cl_2–CH_3OH − H_2O (7:1:0.05, v/v). W3D3 was isolated on reverse phase silica gel column with CH_3OH − H_2O (1:2, v/v) to give two subfractions, W3D3A and W3D3B. Compound **1** (4.0 mg) was cleansed from W3D3A after being subjected to silica gel column with CH_2Cl_2–$(CH_3)_2CO$ (1:1, v/v). Subfraction W3D3B was further isolated on silica gel column with CH_2Cl_2–$(CH_3)_2CO$ (1:1.5, v/v), then by reverse phase silica gel column using $(CH_3)_2CO$ − H_2O (1:2.5, v/v), yielding **3** (2.5 mg). W3D5 was isolated on reverse phase silica gel column with MeOH − H_2O (1:3, v/v) to gain four subfractions, W3D5A-W3D5D. W3D5D was isolated into six fractions W3D5D1-W3D5D6 using reverse phase silica gel column with $(CH_3)_2CO$ − H_2O (1:2, v/v). The purification of W3D5D6 (30 mg) on silica gel column with CH_2Cl_2–$(CH_3)_2CO$ (1:2, v/v), then by reverse phase silica gel column with $(CH_3)_2CO$ − H_2O (1:2.5, v/v), afforded **2** (3.5 mg). W3D4 was separated into four subfractions, W3D4A-W3D4D, after being subjected to reverse phase silica gel column with CH_3OH − H_2O (1:1, v/v). Finally, the cleansing of W3D4B

(30 mg) on HPLC (column: Cosmosil 5C18-MS-II, 250 × 20 mm, 5 µm; flow rate: 2.5 ml/min; CH_3OH − H_2O 58:42) yielded **4** (4.5 mg) and **5** (3.9 mg).

3.2.1. Smallantholide A (1)

Non-crystalline powder; $[\alpha]_D^{20}$ = +57.6 (*c* 0.1, CH_3OH); CD (CH_3OH) λ_{max} (mdeg): 219 (+88.26) nm; ^{13}C NMR (CH_3OH-d_4, 150 MHz) and ^{1}H NMR (MeOH-d_4, 600 MHz): Table S1, view Supplementary data; HR-TOF-MS: *m/z* 283.1536 $[M + H]^+$ (calcd for $C_{15}H_{23}O_5^+$, 283.1540).

3.2.2. Smallantholide B (2)

Non-crystalline powder; $[\alpha]_D^{20}$ = +10.9 (*c* 0.05, CH_3OH); CD (CH_3OH) λ_{max} (mdeg): 219 (+50.09) nm; ^{13}C NMR (CH_3OH-d_4, 150 MHz) and ^{1}H NMR (MeOH-d_4, 600 MHz): Table S1, view Supplementary data; HR-TOF-MS: *m/z* 613.2228 $[M + Na]^+$ (calcd for $C_{30}H_{38}NaO_{12}^+$, 613.2255).

3.2.2. Smallantholide C (3)

Non-crystalline powder; $[\alpha]_D^{20}$ = −42.6 (*c* 0.1, CH_3OH); CD (CH_3OH) λ_{max} (mdeg): 224 (−21.58) nm; ^{13}C NMR (CH_3OH-d_4, 150 MHz) and ^{1}H NMR (MeOH-d_4, 600 MHz): Table S1, view Supplementary data; HR-TOF-MS: *m/z* 408.2018 $[M - H_2O + NH_4]^+$ (calcd for $C_{21}H_{30}NO_7^+$, 408.2017).

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Author contributions

CRediT: **Pham Thi Mai Huong**: Investigation, Writing – original draft; **Do Hoang Anh**: Investigation; **Le Thi Vien**: Investigation; **Tran Thi Hong Hanh**: Data curation, Writing – review & editing; **Nguyen The Cuong**: Data curation, Writing – review & editing, Investigation; **Nguyen Xuan Cuong**: Data curation, Writing – review & editing, Investigation; **Nguyen Hoai Nam**: Supervision, Writing – review & editing.

Disclosure statement

No potential conflict of interest was reported by the authors.

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Supplementary material

General experimental procedures; HR-TOF mass, 1D and 2D NMR spectra of **1** − **3**.

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