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Two new glycoalkaloids from *Stephania succifera*

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ABSTRACT

Two new glycoalkaloids, manshurienine C (**1**) and 8-oxotetrahy-corydalmine-1-*O*-*β*-D-glucopyranoside (**2**), along with eleven known alkaloids (**3–13**), were isolated from the tubers of *Stephania succifera*. Their structures were elucidated by spectroscopic methods, including NMR and MS spectra. Compounds **5**, **6**, **8**, and **10** showed *in vitro* antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).

1. Introduction

Stephania succifera H. S. Lo et Y. Tsoong (Menispermaceae) is mainly distributed in southern China. The tubers are used in Chinese folk medicine for acesodyne, sedation, and detoxication (The Chinese Academy of Science Flora of China Edition Board, 1996). Several classes of alkaloids have been isolated from *S. succifera*, including aporphine, proaporphine, and protoberberine alkaloids (Chen et al., 1989; He et al., 2017; Semwal et al., 2010). Most of these alkaloids exhibited significant pharmacological effects such as cytotoxic, antibacterial, and analgaesic activities (Yang et al., 2010; Zeng et al., 2017). The continuous search for novel and bioactive compounds from *S. succifera* has led to the isolation of two new glycoalkaloids (**1** and **2**) (Fig. 1) and 11 known alkaloids (**3–13**) (Supplementary Fig. S1). Compound **3** is found in nature for the first time, and compounds **4–5**, **7**, **8**, **11**, and **13** are isolated from this plant for the first time. The isolates were assayed for their antibacterial activities against methicillin-resistant *Staphylococcus aureus* (MRSA). Compounds **5**, **6**, **8**, and **10** showed antibacterial activities.

2. Results and discussion

Compound **1** was obtained as a yellow amorphous powder. Its molecular formula was identified as $C_{22}H_{19}NO_9$ by HRESIMS with an $[M+H]^+$ ion at *m/z* 442.1114 (calcd 442.1133). The IR spectrum exhibited absorption bands for lactam (1668 cm^{-1}) and aromatic groups (1557 and 1417 cm^{-1}). The UV absorptions at 381, 323, 289, 277, 267, and 231 nm resembled those of aristolactam derivatives (Yang et al., 2010; Zhang and Jiang, 2006). The ^{13}C NMR data of **1** (Table 1) showed the presence of 22 carbons, including 14 aromatic carbons (δ_C 105.3 − 148.2), a carbonyl (δ_C 167.2), a methylenedioxy (δ_C 103.2), and a glucopyranosyl group (δ_C 60.9, 70.0, 73.7, 76.2, 76.9, and 104.4). The ^1H NMR data (Table 1) presented a methylenedioxy group at δ_H 6.49 (1H, d, J = 1.0 Hz) and 6.50 (1H, d, J = 1.0 Hz); an aromatic AA'BB' coupling system at δ_H 7.66 (1H, dd, J = 7.5, 2.0 Hz, H-6), 7.67 (1H, dd, J = 7.5, 2.0 Hz, H-7), 8.59 (1H, dd, J = 7.5, 2.0 Hz, H-5), and 8.62 (1H, dd, J = 7.5, 2.0 Hz, H-8); a typical amide proton at δ_H 10.10 (s, 1 H); and a singlet aromatic proton at δ_H 7.68 (1H, s, H-2). Further examination of the ^1H-NMR spectrum of **1** revealed the presence of the glucopyranosyl moiety, which should be in a *β*-configuration based on the coupling constant (8.0 Hz) of the anomeric proton (H-1′). The absolute configuration was assigned as D-form by comparing the TLC and optical rotation value between the enzymatic hydrolysis product of **1** and the authentic standards (D-glucose and L-glucose). Therefore, it was concluded that this compound was an aristolactam derivative with a *β*-D-glucopyranose. When comparing the ^1H- and ^{13}C-NMR data of **1** with those of manshurienine A and manshurienine B (Zhang and Jiang, 2006), the only difference was that the glucose of compound **1** was attached at C-9 (δ_C 132.1), which was confirmed by the HMBC correlation (Fig. 2) from H-1′ (δ_H 4.82) to the aromatic carbon C-9. A combination of the HMBC and HSQC experiments permitted the assignment of all protonated carbons. Thus, compound **1** was elucidated as aristolactam II-9-*O*-*β*-D-glucopyranoside and given the trivial name manshurienine C.

Compound **2** was obtained as a yellow amorphous solid. The molecular formula was assigned as $C_{26}H_{31}NO_{11}$ by HRESIMS (*m/z* 534.1950 $[M+H]^+$, calcd 534.1970). The IR spectrum exhibited absorption bands for lactam (1630 cm^{-1}) and aromatic groups (1618 and

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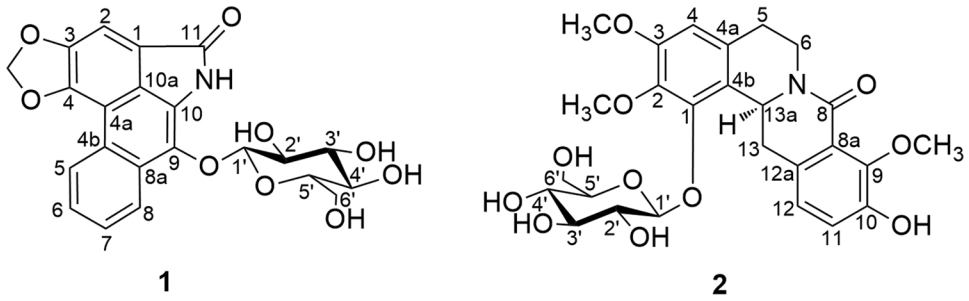

Fig. 1. Structures of compounds **1** and **2** from *Stephania succifera*.

Table 1
^{1}H and ^{13}C NMR spectroscopic data of **1** and **2** (δ in ppm).

No.	**1**		No.	**2**	
	δ_C[a]	δ_H[a] (J in Hz)		δ_C[b]	δ_H[b] (J in Hz)
1	118.6		1	148.6	
2	105.3	7.68, s	2	141.8	
3	148.2		3	153.9	
4	146.8		4	107.8	6.79, s
4a	108.8		4a	133.2	
4b	125.1		4b	124.0	
5	126.1	8.59, dd (7.5, 2.0)	5	25.1	α 2.57, ddd (16.1, 12.5, 4.5)
6	126.4	7.66, dd (7.5, 2.0)			β 3.36, overlapped
7	127.5	7.67, dd (7.5, 2.0)	6	39.4	α 2.83, td (12.5, 2.9)
8	123.7	8.62, dd (7.5, 2.0)			β 4.90, ddd (12.5, 4.5, 2.9)
8a	130.1		8	164.9	
9	132.1		8a	123.0	
10	122.1		9	149.5	
10a	126.0		10	151.5	
11	167.2		11	120.9	7.00, d (8.1)
-OCH_2O-	103.2	6.50, d (1.0)	12	124.0	6.95, d (8.1)
		6.49, d (1.0)			
N-H		10.10, s	12a	131.8	
1′	104.4	4.82, d (8.0)	13	39.7	α 3.16, dd (15.5, 3.0)
2′	73.7	3.46, m			β 2.74, t (15.5)
3′	76.2	3.36, m	13a	56.8	4.79, dd (13.3, 3.0)
4′	70.0	3.23, dd (8.0, 5.1)	1′	105.2	4.98, d (7.5)
5′	76.9	3.29, m	2′	75.7	3.47, overlapped
6′	60.9	3.82, dt (11.3, 4.2)	3′	78.0	3.44, overlapped
		3.51, dt (11.3, 6.0)	4′	71.6	3.39, m
Glc-OH		5.79, d (5.5)	5′	78.2	3.19, m
Glc-OH		5.22, d (4.9)	6′	62.6	3.77, dd (11.9, 5.3)
Glc-OH		5.13, d (5.4)			3.65, dd (11.9, 2.3)
6′-OH		5.16, dd (6.0, 4.2)	2-OCH_3	61.7	3.85, s
			3-OCH_3	56.7	3.86, s
			9-OCH_3	62.0	3.84, s

[a] Measured at 600 MHz (^{1}H) and 150 MHz (^{13}C) in DMSO-d_6.
[b] Measured at 600 MHz (^{1}H) and 150 MHz (^{13}C) in methanol-d_4.

1497 cm^{-1}). The ^{13}C NMR data of **2** (Table 1) showed the presence of 26 carbons, including 12 aromatic carbons (δ_C 107.8 − 153.9), a carbonyl (δ_C 164.9), three methoxy groups (δ_C 56.7, 61.7, and 62.0), three methylenes (δ_C 39.7, 39.4, and 25.1), a methine (δ_C 56.8), and a glucopyranosyl group (δ_C 62.6, 71.6, 75.7, 78.0, 78.2, and 105.2). The ^{1}H NMR spectrum revealed the presence of two *ortho*-coupled aromatic protons at δ_H 6.95 (1H, d, J = 8.1 Hz, H-12) and 7.00 (1H, d, J = 8.1 Hz, H-11); one singlet aromatic proton at δ_H 6.79 (1H, s, H-4); three methoxy groups at δ_H 3.86, 3.85, and 3.84 (each 3H, s). The glucosyl unit with its anomeric proton appearing at δ_H 4.98 (1H, d, J = 7.5 Hz, H-1′) was speculated as a β-configuration. Therefore, an oxoprotoberberine with a glucosyl moiety was proposed. A comparison of the ^{1}H- and ^{13}C-NMR data with those of (-)-8-oxo-10-hydroxy-2,3,9-trimethoxyberberine revealed that compound **2** had an additional glucosyl moiety attached at C-1. The location of the β-glucosyl moiety was supported by the HMBC correlation (Fig. 3) of H-1′ (δ_H 4.98) with C-1 (δ_C 148.6). Enzymatic hydrolysis of compound **2** afforded its sugar and aglycone moieties. The sugar moiety was assigned as D-glucose by comparing the TLC and optical rotation data with those of the authentic standards (D-glucose and L-glucose). The absolute configuration at C-13a was confirmed as *S* (*α*-orientation) by comparing the negative optical rotation ([α]25D –71.1°) of the aglycone moiety with the literature value for this aglycone (Lee et al., 2009). A typical ^{1}H NMR signal at δ_H 4.79 (1H, dd, J = 13.3, 3.0 Hz, H-13a) also supported the *S* configuration at C-13a (Lee et al., 2009). Thus, compound **2** was deduced as (-)-8-oxo-10-hydroxy-2,3,9-trimethoxyberberine-1-*O*-*β*-D-glucopyranoside, which could also be named as (-)-8-oxotetrahy-corydalmine-1-*O*-*β*-D-glucopyranoside.

The known compounds (**3**–**13**) (Supplementary Fig. S1) were identified as secocrebanine (**3**) (Wang et al., 2016), norcrebanine (**4**) (Rayanil et al., 2016), 8-hydroxy-9-methoxy-1,2-methylenedioxyaporphine (**5**) (Thuy et al., 2012), crebanine (**6**) (Makarasen et al., 2011), *N*-formyl-asimilobine-2-*O*-*β*-D-glucopyranoside (**7**) (Choudhary et al., 2010), asimilobine-2-*O*-*β*-D-glucopyranoside (**8**) (Likhitwitayawuid et al., 1993), *N*-methylasimilobine-2-*O*-*β*-D-glucopyranoside (**9**) (Kashiwaba et al., 2000), asimilobine (**10**) (Costa

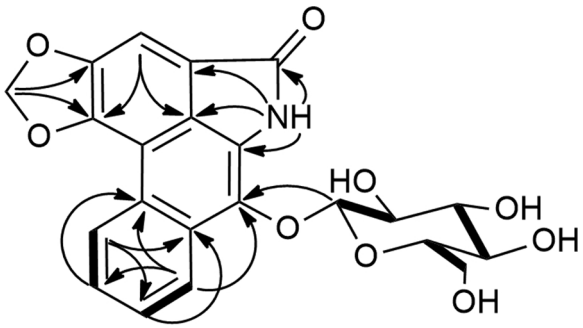

Fig. 2. Selected ^{1}H–^{1}H COSY (H—H) and HMBC (H→C) correlations of compound **1**.

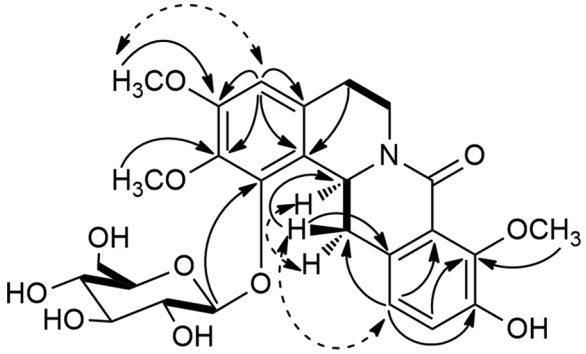

Fig. 3. Selected ^{1}H–^{1}H COSY (H—H), HMBC (H→C), and ROESY (H⇜⇝H) correlations of compound **2**.

et al., 2015), liriodenine (**11**) (Fujita et al., 2010), 4-hydroxycrebanine (**12**) (Kunitomo et al., 1985), and *trans*-feruloyl-(3-*O*-methyl)-dopamine-4-*O*-*β*-D-glucopyranoside (**13**) (Yim et al., 2012) by comparison of experimental and reported spectroscopic data. Compound **3** is found in nature for the first time, and compounds **4**, **5**, **7**, **8**, **11**, and **13** are isolated from *S. succifera* for the first time.

All isolated compounds were tested for their *in vitro* antibacterial activity against MRSA by the broth microdilution method. Vancomycin was used as a positive control. As shown in Table 2, compounds **5**, **6**, **8**, and **10** showed antimicrobial activity against MRSA. The lowest minimum inhibitory concentration (MIC) was observed for compound **6** (128 *μ*g/mL) followed by compounds **5**, **8**, and **10** (256 *μ*g/mL).

Table 2
Anti-MRSA activities of the compounds isolated from *S. succifera*.

Compounds	MIC(*μ*g/mL)
manshurienine C **(1)**	> 256
8-oxotetrahy-corydalmine-1-*O*-*β*-D-glucopyranoside **(2)**	> 256
secocrebanine **(3)**	> 256
norcrebanine **(4)**	> 256
8-hydroxy-9-methoxy-1,2-methylenedioxyaporphine **(5)**	256
crebanine **(6)**	128
N-formyl-asimilobine-2-*O*-*β*-D-glucopyranoside **(7)**	> 256
asimilobine-2-*O*-*β*-D-glucopyranoside **(8)**	256
N-methylasimilobine-2-*O*-*β*-D-glucopyranoside **(9)**	> 256
asimilobine **(10)**	256
liriodenine **(11)**	> 256
4-hydroxycrebanine **(12)**	> 256
trans-feruloyl-(3-*O*-methyl)-dopamine- 4-*O*-*β*-D-glucopyranoside **(13)**	> 256
vancomycin[a]	0.5

[a] Vancomycin was used as a positive control.

3. Material and methods

3.1. General experimental procedures

Optical rotations were recorded using a Rudolph Autopol IV–T autometic polarimeter (Rudolph Research Analytical, USA). UV spectra were measured on a U–2900 spectrophotometer (Hitachi, Japan). IR spectra were obtained on a Nicolet i5 spectrometer (Thermo Fisher, USA) with KBr pellets. HRESIMS spectra were recorded on a TripleTOF 5600+ mass spectrometer (Applied Biosystems Sciex, USA). NMR spectra were recorded on a Bruker Ascend™ 600 MHz spectrometer with TMS as internal standard. Column chromatography (CC) was performed using silica gel (200–300 and 300–400 mesh, Qingdao Haiyang Chemical Co., Ltd., China), HZ818 macroporous resin (HuaZhen Technology, China), C_{18} (40–60 μm, Agela Technologies, China), and Sephadex LH–20 (Amersham Biosciences, Sweden). Fractions were monitored by TLC using precoated GF254 silica gel plates (Qingdao Haiyang Chemical Co., Ltd., China) and RP–18 $F_{254}S$ silica gel plates (Merck KGaA, Germany). Semipreparative HPLC was carried out on an LC–15C (Shimadzu, Japan) with a Gemini C_{18} column (10 mm × 150 mm, 5 μm, Phenomenex, Germany).

3.2. Plant material

The tubers of *S. succifera* were collected at Wuzhishan, Hainan Province, China, in 2014, and authenticated by Dr. Yun Kang, Fudan University. A voucher specimen (2014057 G) has been deposited in the Department of Pharmacognosy, Fudan University, China.

3.3. Extraction and isolation

The dried and powdered tubers (5.5 kg) of *S. succifera* were extracted with 95% EtOH (50 L) at room temperature. After concentration under reduced pressure, the crude extract (798 g) were dissolved in water (2 L) to get a homogeneous dispersion and then partitioned successively with petroleum ether (PE) and dichloromethane (CH_2Cl_2) to afford a PE extract (85 g) and a CH_2Cl_2 extract (196 g). The remaining aqueous solution was applied to an HZ818 macroporous resin column eluted with EtOH–H_2O (95:5, v/v). The EtOH–H_2O (95:5) eluate (99 g) was chromatographed on a silica gel column (200–300 mesh) with a gradient CH_2Cl_2–MeOH (15:1, 10:1, 5:1, 2:1, 0:1, v/v) as eluent to give nine fractions (Fr. A–I). Fr.G was loaded on another HZ818 macroporous resin column eluted with a gradient MeOH–H_2O (5:5, 6:4, 7:3, 1:0, v/v) to yield subfractions G1–G5. Fr.G3 was subjected to C_{18} CC eluted with MeOH–H_2O (3:7, 4:6, 5:5, 6:4, 1:0, v/v) to give Fr.G3.1 to Fr.G3.5. Fr.G3.2 was further separated on a Sephadex LH-20 CC (MeOH) followed by semipreparative HPLC (MeOH–H_2O, 45:55, v/v, flow rate 3 mL/min) to yield **2** (5.4 mg) and **7** (10.0 mg). Fr.G3.3 was purified by Sephadex LH-20 CC (MeOH) and semipreparative HPLC (MeOH–H_2O, 35:65, v/v, flow rate 3 mL/min) to yield **13** (2.7 mg). Fr.G4 was subjected to silica gel CC (300–400 mesh) eluted with a gradient CH_2Cl_2–MeOH (15:1, 10:1, 8:1. 5:1, v/v) and further purified by semipreparative HPLC (MeOH–0.05% Et_2NH aqueous solution, 40:60, v/v, flow rate 3 mL/min) to give **10** (12.9 mg). Fr.G5 was purified by Sephadex LH-20 CC (MeOH) and semipreparative HPLC (MeOH–H_2O, 55:45, v/v, flow rate 3 mL/min) to yield **1** (2.4 mg). Fr.H was subjected to semipreparative HPLC (MeOH–0.02% Et_2NH aqueous solution, 30:70, v/v, flow rate 3 mL/min) to yield **8** (6.8 mg). Compound **9** (5.1 mg) was obtained from Fr.I using the same procedure as compound **8**. The CH_2Cl_2 extract was fractionated on a silica gel CC (200–300 mesh) using a gradient CH_2Cl_2–MeOH (1:0, 50:1, 20:1, 10:1, 1:1, 0:1, v/v) as eluent to give eight fractions (Fr.J–Q). Fr.L was loaded on another silica gel CC (300–400 mesh) eluted with a gradient CH_2Cl_2–MeOH (30:1, 20:1, 10:1, v/v) to give subfractions L1–L6. Fr.L3 was purified by Sephadex LH-20 CC (MeOH) followed by semipreparative HPLC (MeOH–0.02% Et_2NH aqueous solution, 88:12, v/v,

flow rate 3 mL/min) to yield **6** (18.7 mg). Fr.L4 was subjected to C_{18} CC eluted with MeOH–H_2O (1:4, 1:1, 7:3, 9:1, 1:0, v/v) to give Fr.L4.1 to Fr.L4.5. Fr.L4.3 was separated by semipreparative HPLC (flow rate 3 mL/min) eluted with MeOH–0.02% Et_2NH aqueous solution (90:10, v/v), MeOH–0.02% Et_2NH aqueous solution (85:15, v/v), and CH_3CN–0.02% Et_2NH aqueous solution (6:4, v/v) to afford **4** (8 mg), **5** (4.9 mg), and **12** (33 mg), respectively. Fr.L4.4 was purified by Sephadex LH-20 CC (MeOH) followed by semipreparative HPLC (MeOH–0.02% Et_2NH aqueous solution, 60:40 and 95:5 for the purification of **3** and **11**, respectively, v/v, flow rate 3 mL/min) to yield **3** (2.1 mg) and **11** (1.8 mg).

3.4. Spectroscopic data

3.4.1. manshurienine C (1)

Yellow amorphous powder; [α]25D –155.0° (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε): 381 (3.59), 323 (3.75), 289 (4.17), 277 (4.22), 267 (4.21), 231 (4.26) nm; IR (KBr) ν_{max} 3734, 3703, 3627, 3595, 1668, 1557, 1417, 1288, 1071 cm^{-1}; ^1H and ^{13}C NMR data see Table 1; HRESIMS *m/z* 442.1114 $[M+H]^+$ (calcd for $C_{22}H_{19}NO_9$, 442.1133).

3.4.2. 8-oxotetrahy-corydalmine-1-O-β-D-glucopyranoside (2)

Yellow amorphous solid; [α]25D –179.0° (*c* 0.10, MeOH); UV (MeOH) λ_{max} (log ε): 278 (4.07) nm; IR (KBr) ν_{max} 3643, 2938, 2334, 1630, 1618, 1497, 1483, 1331, 1026, 666 cm^{-1}; ^1H and ^{13}C NMR data see Table 1; HRESIMS: *m/z* 534.1950 $[M+H]^+$ (calcd for $C_{26}H_{31}NO_{11}$, 534.1970).

3.5. Enzymatic hydrolysis of compounds 1 and 2

The enzymatic hydrolysis was performed based on a previously reported method (Cong et al., 2014). Compounds **1** and **2** (1 mg) were separately dissolved in H_2O (500 μL) and mixed with β-cellulase (2 mg). The mixtures were kept at 37℃ for 2 days and then extracted with EtOAc. The EtOAc layer of compound **2** was concentrated to dryness under reduced pressure and redissolved with methanol (1 mL) for optical rotation measurement of the aglycone moiety. The aqueous phases were used for optical rotation measurement and TLC analysis of the sugar moieties. The liberated sugars of **1** and **2** were confirmed as glucose because of the same R_f value (0.35) in TLC (EtOAc: MeOH: H2O: HOAc = 13:3:3:4) as the authentic standards (D-glucose and L-glucose), and were identified as D-form based on their nearly identical optical rotation values to the D-glucose standard ([α]25D +52.6°).

3.6. Antibacterial assay

The isolated compounds were tested for *in vitro* antibacterial activities against MRSA strains ATCC 43,300 (American Type Culture Collection (ATCC), USA) by the broth microdilution method (Luo et al., 2014). The compounds and vancomycin (positive control) were dissolved in methanol, respectively, diluted in cation-adjusted Mueller Hinton broth (CAMHB) to achieve nine twofold serially diluted concentrations, and then added to the wells of microtiter plates. For inoculum preparation, conidial suspensions were harvested from cultures incubated for 24 h at 37℃ in Mueller Hinton Agar medium (MHA). The bacterial suspensions were adjusted to a working inoculum concentration of 1×10^6 CFU/mL. A 100 μL aliquot of the inoculum was dispensed into the microdilution wells (except for negative control well). The microplates were incubated at 37℃ for 20 h. If the compound inhibited bacterial growth, the incubation solution appeared clear. The minimum inhibitory concentration (MIC) was recorded as the lowest concentration at which no bacterial growth was observed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

There are no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.phytol.2019.10.001.

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