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SHORT COMMUNICATION

A new cardenolide glycoside from the roots of *Streptocaulon juventas* (lour.) merr. (Asclepiadaceae)

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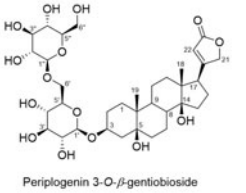
ABSTRACT

From remaining aqueous fraction of the roots of *Streptocaulon juventas*, one new cardiac glycoside named periplogenin 3-*O*-β-gentiobioside (**1**) together with six known ones (**2–7**) were isolated. Their relative structures were elucidated based on NMR spectroscopic analysis. Compound **1** showed moderate cytotoxicity against non-small cell lung carcinoma NCI-H460 and ovarian cancer HeLa cells. Moreover, compounds **2** and **3** exhibited remarkable cytotoxicity against NCI-H460 cell with the IC_{50} values of 0.34 and 0.068 μM, respectively.



Periplogenin 3-*O*-β-gentiobioside

Compound	Growth Inhibition (%)		
	NCI-H460	HeLa	MCF-7
1	71.87	60.16	47.72

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Streptocaulon juventas; Asclepiadaceae; cardiac diglycoside; cytotoxicity

1. Introduction

Streptocaulon juventas (Lour.) Merr. (Asclepiadaceae) is mainly found in Indochina. In Vietnam, *S. juventas* is called "*Ha thu o trang*", and its roots are used as a tonic for various conditions such as anemia, chronic malaria, rheumatism, menstrual disorders, neurasthenia, and dyspepsia (Vo 1999). The phytochemical investigation of *S. juventas* has led to the isolation of various cardenolides, hemiterpenes, and phenylpropanoids (Ueda et al. 2003a). Cardenolides are the active components of *S. juventas*, that have

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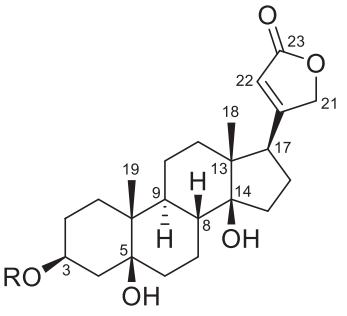

	R
1	Glc^{6}-Glc
2	H
3	Glc
4	Dig^{4}-Glc
5	Cym^{4}-Glc
6	Dtl^{4}-Glc
7	$(2\text{-OAc-Dtl})^{4}$-Glc

Cym: β-D-cymarose
Dig: β-D-digitoxose
Dtl: β-D-digitalose
Glc: β-D-glucose

Figure 1. Structure of compounds 1–7

long been used as cardiotonic drugs (Morsy 2017). Additionally, cardenolides induce apoptosis in human tumor cells with no significant toxicity on normal cells (Ueda et al. 2003b, Xue et al. 2015).

Cardiac glycosides from *S. juventas* showed potent cytotoxicity against human lung A549 adenocarcinoma and non-small lung cancer NCI-H460 cells (Xue et al. 2014). Therefore, further investigation on the remaining aqueous extract of *S. juventas* was carried out, that resulted in the isolation of a new cardiac glycoside, periplogenin 3-*O*-β-gentiobioside (**1**), along with six known ones (**2**–**7**). Details regarding the isolation, structural elucidation, and cytotoxicity of **1**–**7** are reported herein.

2. Results and discussion

The powdered roots of *S. juventas* were heated at reflux in MeOH. The MeOH-soluble extract was successively partitioned to yield $CHCl_3$-soluble and remaining aqueous fractions. Further separation and purification of the remaining aqueous fraction led to the isolation of seven compounds: periplogenin 3-*O*-β-gentiobioside (**1**), periplogenin (**2**) (Ueda et al. 2003a), periplogenin 3-*O*-β-D-glucopyranoside (**3**) (Kawaguchi et al. 1988), corchorusoside C (**4**) (Nakamura et al. 1998), periplocin (**5**) (Sakuma et al. 1971), periplogenin 3-*O*-[*O*-β-D-glucopyranosyl-(1➔4)-*O*-β-D-digitalopyranoside] (**6**) (Ueda et al. 2003a), and periplogenin 3-*O*-[*O*-β-D-glucopyranosyl-(1➔4)-2-*O*-acetyl-β-D-digitalopyranoside] (**7**) (Myint Khine et al. 2004) (Figure 1).

Compound **1**, periplogenin 3-*O*-β-gentiobioside, showed a *quasi*-molecular ion peak at *m/z* 713.3389 $[M-H]^-$ (calcd for $C_{35}H_{53}O_{15}$, 713.3384) in the HRESIMS. The ^1H NMR spectrum showed the presence of two methyl singlets [δ_H 0.97 (s, Me-18) and 1.00 (s,

Table 1. Cytotoxicity of the isolated compounds (at concentration of 100 μg mL^{-1}) against NCI-H460, HeLa, and MCF-7 cells.

	Growth Inhibition (%)		
Compounds	NCI-H460	HeLa	MCF-7
1	71.87 ± 2.31	60.16 ± 0.48	47.72 ± 5.77
2	89.66 ± 0.50	73.75 ± 3.70	69.56 ± 2.60
3	89.25 ± 0.30	84.02 ± 2.10	72.86 ± 7.40
4	87.33 ± 2.45	69.54 ± 5.52	83.88 ± 3.15
5	87.54 ± 1.02	80.60 ± 1.58	74.60 ± 5.70
6	87.99 ± 1.85	73.69 ± 4.41	80.83 ± 3.53
Camptothecin	77.90 ± 2.30[a]	49.57 ± 1.25[β]	47.00 ± 1.86[α]

[a]at concentration of 0.01 μg mL^{-1}.
[b]at concentration of 1 μg mL^{-1}.

Me-19)], an α,β-unsaturated-γ-lactone moiety [δ_H 6.12 (brs, H-22), 5.03 (d, $J = 18.0$ Hz, H-21a), 5.28 (d, $J = 18.0$ Hz, H-21b)], one oxymethine proton [δ_H 4.52 (m, H-3)], and one methine proton [δ_H 2.80 (dd, $J = 8.5$ and 5.0 Hz, H-17)]. Additionally, two anomeric protons [δ_H 4.92 (d, $J = 7.5$ Hz, H-1′) and 5.02 (d, $J = 8.0$ Hz, H-1″)] and two oxymethylene groups [δ_H 4.79 (d, $J = 11.0$ Hz, H-6′a), 4.25 (m, H-6′b), 4.45 (d, $J = 10.5$ Hz, H-6″a), 4.27 (m, H-6″b)] were indicated the presence of two β-glucopyranose moieties. The ^{13}C and DEPT NMR spectra showed resonances for one ester carbonyl carbon (δ_C 174.6), one pair of olefinic carbons (δ_C 176.0, 117.6), two acetal carbons (δ_C 101.6, 105.3), three oxymethylene carbons (δ_C 73.8, 70.2, 62.8), nine oxymethine carbons (δ_C 78.6, 2 × 78.4, 77.4, 75.2, 75.0, 74.4, 2 × 71.7), two oxygenated tertiary carbons (δ_C 84.7, 73.2), three methine carbons (δ_C 51.3, 40.9, 39.2), nine methylene carbons (δ_C 40.0, 36.2, 34.1, 33.2, 27.3, 26.6, 26.1, 24.5, 22.0), two quaternary carbons (δ_C 50.0, 41.2), and two methyl carbons (δ_C 17.2, 16.1) (Table S1). These signals were consistent with those reported for a periplogenin diglycoside comprising a 17β-lactone unit (Gil et al. 1995) and two β-glucopyranose moieties (Agrawal 1992). Based on the paired ^1J coupling responses in the HMBC spectrum (Figure S7), the measured $J_{C\text{-}1'/H\text{-}1'}$ and $J_{C\text{-}1''/H\text{-}1''}$ values of 157.6 and 157.4 Hz, respectively, were consistent with the anomeric axial bond of β-gentiobiose octaacetate ($J_{C/H}$ = 162.0 Hz in $CDCl_3$) (Tvaroska and Taravel 1995), which is a disaccharide composed of two units of D-glucose joined with a β(1➔6) linkage (Reynolds and Evans 1938). The D-configurations of two glucosyl moieties were attempted to define based on the acid-catalyzed hydrolysis and the specific rotations of resulting sugars (Xue et al. 2013). Due to the small isolated amount of **1**, few resulting sugars were obtained to measure the optical rotations. On the other hand, compound **1** showed $[\alpha]_D^{25}$ value of −36.2 (*c* 0.05, MeOH), in comparison with those of digitoxigenin 3-*O*-β-D- and 3-*O*-β-L-glucopyranosides ($[\alpha]_D^{25}$, −6.30 and +16.33 (*c* 0.3, MeOH), respectively) (Rathore et al. 1985), to deduce the D-configuration of two glucose moieties. The steroidal tetracyclic skeleton was verified by using the ^1H–^1H COSY correlations between H-1/H-2/H-3/H-4, H-6/H-7/H-8/H-9/H-11/H-12, H-15/H-16/H-17 and HMBC correlations between Me-18/C-12/C-14/C-17, Me-19/C-1/C-5/C-9 (Figure S1). The α,β-unsaturated-γ-lactone ring at C-17 was indicated based on HMBC correlations between H-17/C-20/C-21. The 1′,3- and 1″,6′-glycosidic linkages were indicated based on the HMBC correlations between H-1′/C-3, H-1″/C-6′, and H-6′/C-1″. The ^{13}C NMR chemical shift of Me-19 (δ_C 17.2) in **1** closely resembled with those of periplogenin (5β-OH cardenolide) glycosides (Robien et al. 1987). In 5α-cardenolides, C-9 has its

signal at δ_C 45.2–53.9 ppm (Robien et al. 1987) whereas in **1** at upfield region δ_C 39.2 ppm; therefore the *cis* A/B ring fusion for **1** was established. It was confirmed based on the NOESY correlations between H-1/Me-19 and H-2/H-9. The NOESY correlations between Me-19/H-8/Me-18 indicated the relative configuration of rings B/C and C/D were *trans*- and *cis*-fused, respectively (Figure S1). Based on the ^{13}C NMR chemical shift of C-4 (δ_C 36.9 in periplogenin and δ_C 41.3 in 3-*epi*-periplogenin) (Peter and Max 1980), it was supported the presence of C-3 β-substituted of **1** ($\delta_{C\text{-}4}$ 36.9 in **1**). Moreover, the presence of two β-D-glucopyranose moieties was affirmed based on the NOESY spectrum. Thus, the relative structure of periplogenin 3-*O*-β-gentiobioside (**1**) was assigned as shown.

All isolated compounds, except for **7** due to the meager amount isolated, were tested for their cytotoxicity against non-small cell lung carcinoma NCI-H460, ovarian cancer HeLa, and breast cancer MCF-7 cells (Table 1). These compounds at a concentration of 100 μg mL^{-1} showed more than 70% cytotoxicity against NCI-H460 cell line. At the same concentration, all isolated compounds produced more than 60% and 45% cytotoxic effect against HeLa and MCF-7 cells, respectively. In this regard, compound **1** showed moderate cytotoxicity (71.87% and 60.16% growth inhibition) against NCI-H460 and HeLa cells, respectively. Compounds **2** and **3** exhibited remarkable cytotoxicity (approx. 90% growth inhibition) against NCI-H460 non-small cell lung cancer cells. Thus, their cytotoxicities at various concentrations were evaluated to obtain the IC_{50} values of 0.34 and 0.068 μM, respectively. Camptothecin was used as a positive control, with an IC_{50} value of 0.0086 μM.

3. Experimental

3.1. General experimental procedures

Optical rotations were measured on an A. Krüss Optronic polarimeter P3000 (Krüss Optronic GmbH, Hamburg, Germany). Optical density values were determined with a 96-well microtiter plate reader (Synergy HT, Biotek Instruments). The IR spectra were measured with a Shimadzu IR-408 infrared spectrometer (Shimadzu Pte., Ltd.). The NMR spectra were recorded on a Bruker Avance III 500 spectrometer (Bruker BioSpin AG, Bangkok) with pyridine-d_5 as a solvent, and the chemical shifts are expressed as δ values. HRESIMS data were acquired on Bruker micrOTOF QII (Bruker Singapore Pte., Ltd.) mass spectrometer. Column chromatography was carried out using silica gel 60, 0.06–0.2 mm (Scharlau, Barcelona) and LiChroprep® RP-18, 40 – 63 μm (Merck KGaA, Darmstadt). Analytical and preparative TLCs were carried out on precoated Kieselgel 60 F_{254} or RP_{18} plates (Merck KGaA, Darmstadt).

3.2. Plant material

The roots of *Streptocaulon juventas* (Lour.) Merr. was collected at An Phu Commune, Tinh Bien District, An Giang Province, Vietnam, in October 2007 and was identified by MSc. Viet Hoang, Department of Ecology and Evolutionary Biology, Faculty of Biology and Biotechnology, VNUHCM–University of Science. A voucher specimen (DOC2007-

HTOT) has been deposited at the Department of Organic Chemistry, Faculty of Chemistry, VNUHCM–University of Science.

3.3. Extraction and isolation

The powdered roots of *S. juventas* (8 kg) were refluxed with MeOH (30 L, 3 h × 3) to obtain the MeOH-soluble extract (850 g). This extract was suspended in H_2O and successively partitioned with $CHCl_3$ (2.5 L) to give the $CHCl_3$-soluble (191 g) and remaining aqueous (about 720 g, not dry completely) fractions. The aqueous fraction was subjected to a Diaion HP-20 column chromatography and eluted with H_2O–MeOH (v/v, 100:0, 75:25, 50:50, 25:75, 0:100) mixtures, to obtain 5 fractions (Fr.1 – 5). Fraction Fr.3 (29.6 g) was separated over a silica gel column with H_2O–MeOH–$CHCl_3$ (v/v, 0.1:1:9 ➔ 1:4:6) mixtures, to give 5 subfractions (Fr.3.1 – 3.5). Subfraction Fr.3.3 (9.9 g) was chromatographed over a silica gel column with H_2O–MeOH–$CHCl_3$ (v/v, 0.2:2:8 ➔ 1:5:10) mixtures and purified by RP-18 silica gel with H_2O–MeOH–MeCN (4:1:1), to afford **4** (5.5 mg) and **5** (6.5 mg). Subfraction Fr.3.4 (1.1 g) was passed over a silica gel column eluted with H_2O–MeOH–$CHCl_3$ (v/v, 0.2:2:8 ➔ 1:5:10) mixtures and purified by preparative RP-18 TLC with H_2O–MeCN (2:1), to afford **1** (3.8 mg). Fraction Fr.4 (44.6 g) was loaded onto a silica gel column and eluted with H_2O–MeOH–$CHCl_3$ (v/v, 0.2:2:8 ➔ 1:6:14) mixtures, to yield 5 subfractions (Fr.4.1 – 4.5). Subfraction Fr.4.1 (10.3 g) was subjected to silica gel column chromatography eluted with H_2O–MeOH–$CHCl_3$ (v/v, 0.1:1:9 ➔ 0.2:2:8) mixtures and further separated by RP-18 silica gel with H_2O–MeCN (3:2), to afford **2** (15 mg). Subfraction Fr.4.2 (14.2 g) was chromatographed over a silica gel column with H_2O–MeOH–$CHCl_3$ (v/v, 0.1:1:9 ➔ 1:6:14) mixtures and followed by a RP-18 silica gel column with H_2O–MeOH–MeCN (3:2:1), to obtain **3** (6.5 mg). Subfractions Fr.4.3 (5.6 g) and Fr.4.4 (1.6 g) were subjected to silica gel column chromatography eluted with (v/v, 0.2:2:8 ➔ 1:5:10) mixtures and further purified by preparative RP-18 TLC with H_2O–MeCN (2:1) and H_2O–MeOH–MeCN (4:1:1), to afford **6** (5 mg) and **7** (2 mg), respectively.

3.3.1. Periplogenin 3-O-*β*-gentiobioside *(1)*

White amorphous solid; IR (KBr) ν_{max} 3445, 1741, 1623 cm^{-1}; $[\alpha]_D^{25}$ −36.2 (*c* 0.05, MeOH); ^1H (500 MHz, C_5D_5N) and ^{13}C NMR (125 MHz, C_5D_5N), see Table S1; HRESIMS *m/z* 713.3389 $[M-H]^-$ (calcd for $C_{35}H_{53}O_{15}$, 713.3384).

3.4. Acid-Catalyzed hydrolysis of 1

An aliquot (2 mg) of compound **1** in 1 N HCl (1,4-dioxane–H_2O, 1:1; 1.5 mL) was heated at 90 °C for 24 h. The resulting mixture was diluted with 5 mL of water. The aqueous solution was extracted with EtOAc (3 × 3 mL), and the aqueous phase was neutralized with 1 N KOH. After removal of solvent, 0.3 mg of glucose was obtained. TLC identification was performed using $CHCl_3$–CH_3OH–H_2O (60:30:5), in comparison with that of an authentic sample of glucose. Due to the small amount of resulting sugar, its optical rotation could not be determined.

3.5. Cell lines and cell culture

NCI-H460 (HTB-177), MCF-7 (HTB-22), and HeLa (CCL-2) cells were purchased from the American Type Culture Collection (Manassas, Rockville). Cells were cultured at 37 °C and 5% CO_2 in Eagle's Minimal Essential Medium (EMEM) supplemented with 10% (v/v) FBS (Sigma-Aldrich), 2 mM L-glutamine (Sigma-Aldrich), 20 mM HEPES (Sigma-Aldrich), 0.025 μg mL^{-1} amphotericin B (Sigma-Aldrich), 100 IU mL^{-1} penicillin G (Sigma-Aldrich), and 100 μg mL^{-1} streptomycin (Sigma-Aldrich).

3.6. Sulforhodamine B (SRB) cytotoxicity assay

The assay was performed as previously described with some modifications (Vistica et al. 1990). Cells were seeded at a density of 10,000 cells/well (MCF-7, HeLa) or 7,500 cells/well (NCI-H460) in 96-well plates. Cells were cultured for 24 h before being incubated with isolated compounds at different concentrations for 48 h. Treated cells were fixed with cold 50% (w/v) trichloroacetic acid (Merck KGaA) for 1–3 h, washed, and stained with 0.2% (w/v) SRB (Sigma-Aldrich) for 20 min. After five washes with 1% acetic acid (Merck KGaA), the protein-bound dye was solubilized in 10 mM Tris base solution (Promega). Optical density values were determined at the wavelengths of 492 nm and 620 nm. The percentage of growth inhibition (Inh %) was calculated according to the formula: Inh % $= (1 - [ODt/ODc] \times 100)$ %, in which ODt and ODc are the optical density value of the test sample and the control sample, respectively. Data were represented as means ± standard error ($n \geq 3$). The IC_{50} values was determined by using Prism software with multivariate nonlinear regression and $R^2 > 0.9$. Camptothecin (Merck KGaA) was used as a positive control.

4. Conclusions

Chemical investigation of the roots of *Streptocaulon juventas*, led to the isolation of seven cardenolide glycosides (**1**–**7**), including a new compound, periplogenin 3-*O*-*β*-gentiobioside (**1**). Compounds **1**–**6** showed potent cytotoxicity against non-small cell lung carcinoma NCI-H460 cell. Moreover, these compounds exhibited moderate growth inhibition against HeLa and MCF-7 cells. Thus, this promising *S. juventas* may be useful as a potential anti-tumor candidate.

Supplementary material

NMR and MS spectra for the new compound **1**.

Disclosure statement

No potential conflict of interest was reported by the authors.

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