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SHORT REPORT

Cytotoxic phloroglucinol glucosides from microalgae (*Spirulina platensis*)

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Abstract: Two new phloroglucinol glucosides, spiruplatosides A (**1**) and B (**2**) along with six known compounds, including 5,7-dimethoxyflavone (**3**), 5-hydroxy-7,4′-dimethoxyflavone (**4**), 5,7,4′-dimethoxyflavone (**5**), terephthalic acid dimethyl ester (**6**), terephthalic acid-(2-hydroxyethyl ester)-methyl ester (**7**), 13*S*-hydroxy-9*Z*,11*E*-octadecadienoic acid (**8**) were isolated from the microalgae *Spirulina platensis*. Compounds **1–8** were evaluated for cytotoxic activity against SK-LU-1 and HepG2 cancer cells. Compounds **1** and **2** were the most active with IC_{50} values ranging from 1.40 to 3.66 µM. Compounds **4** and **5** showed moderate effects with IC_{50} values ranging from 66.09 to 74.46 µM.

Keywords: *Spirulina platensis*, microalgae, spiruplatoside, phloroglucinol glucoside, cytotoxic activity

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1 Microalgae Source

The *Spirulina platensis* NA12 strain was isolated from aquaculture ponds in Nghe An Province, Vietnam (19.186797°N, 105.707979°E) in November 2024. Individual filaments were separated under an inverted microscope (Olympus CK40) using a sterilized Pasteur pipette with a flame-narrowed, smooth tip. Each filament was rinsed several times in drops of sterile Zarrouk medium to remove contaminating cells and particles and then transferred onto sterile Zarrouk agar (1.5% w/w) plates.

The morphology of the *S. platensis* NA12 strain was examined using a light microscope with an attached, charge-coupled device camera (Nikon Eclipse 55i). The *S. platensis* NA12 strain was identified according to its morphological characteristics with standard manual taxonomic references for Cyanobacteria (Komárek & Anagnostidis, 2005).

2 Previous Studies

The chemical profile of *S. platensis* is characterized by high protein content and secondary metabolites such as fatty acids (de Oliveira et al., 1999), phycocyanins (Antelo et al., 2008), carotenoids, flavonoids and polyphenols (Ferdous & Balia Yusof, 2021). In addition, the extract and compounds from *Spirulina* genus exhibited cytotoxic, anti-inflammatory (Ngu et al., 2022), and antibacterial activities (Kaushik & Chauhan, 2008). This study reports the isolation and structure elucidation of two new phloroglucinol glucosides and six known compounds. The cytotoxic activity of all compounds was also evaluated.

3 Present Study

The isolated *S. platensis* NA12 strain was cultivated in 5 L flasks (20 culture flasks), each containing Zarrouk medium, for a period of 10 days. The cultures were maintained under controlled laboratory conditions with continuous aeration using a sterile air pump, illuminated with LED light at an intensity of 2000 lux under a 12:12 h light–dark photoperiod. The initial medium pH was adjusted to 9.5 using sterile 0.1 M NaOH. Throughout the cultivation period, pH was actively monitored and regulated as continuous aeration and photosynthetic activity gradually increased the medium pH by adding acid (0.1 M HCl). The temperature was maintained within the range of 25–28°C throughout the cultivation period. The grow algal culture was then transferred to 200 L photobioreactor (4 culture units) with an inoculum ratio of 10–15% (v/v). Cultivation was carried out under continuous

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aeration and LED illumination at an intensity of 2000 lux. The culture conditions were maintained at pH 9.0–10 and a temperature range of 25–30°C for 18 days. The biomass of the *S. platensis* NA12 was collected by centrifugation at 10,000× g for 10 min.

The dried biomass of the *S. platensis* (3.0 kg) was ultrasonically extracted with methanol (MeOH) at 40°C three times (each 9.0 L, 3 h). The MeOH layer was evaporated *in vacuo* to give a dark solid residue (200 g). This crude extract was suspended in water (2.0 L) and partitioned with *n*-hexane and CH_2Cl_2 to obtain *n*-hexane (SP1, 15 g), CH_2Cl_2 fractions (SP2, 30 g) and water layer (SP3). The SP2 fraction was separated on a silica gel column chromatography (CC), eluting with *n*-hexane/acetone (20/1, 10/1, 5/1, 2/1, 0/1, v/v) to give four fractions, SP2A (3.1 g), SP2B (4.5 g), SP2C (640 mg), and SP2D (5.4 g).

The SP2B fraction (4.5 g) was chromatographed on a silica gel CC and an eluent of *n*-hexane/EtOAc (5/1, v/v) to give fractions, SP2B1 (1.0 g), SP2B2 (1.5 g), SP2B3 (640 mg), and SP2B4 (300 mg). The SP2B2 fraction was chromatographed on an RP-18 CC eluting with MeOH/water (7/1, v/v) to give three fractions, SP2B2A (100 mg), SP2B2B (85 mg), and SP2B2C (172 mg). The SP2B2A fraction was chromatographed on an HPLC system (eluent of 70% acetonitrile (ACN) in water) to yield compound **6** (40.0 mg, t_R 20.5 min). The SP2B3 fraction was first chromatographed on an RP-18 CC eluting with acetone/water (5/1, v/v) then on an HPLC system (eluent of 80% ACN in water) to yield compound **8** (8.3 mg, t_R 39.0 min). The SP2B4 fraction was chromatographed on an RP-18 CC eluting with acetone/water (5/1, v/v) then on an HPLC (eluent of 68% ACN in water) to yield compound **7** (5.7 mg, t_R 46.9 min).

The aqueous fraction (SP3) was subjected to Diaion HP-20 CC using water to remove sugars and polar fractions then MeOH, affording fraction SP3A (80.0 g). SP3A was chromatographed on a silica gel CC, eluted with CH_2Cl_2/MeOH (20/1, 10/1, 5/1, 2.5/1, v/v), yielding four fractions, SP3A1 (300 mg), SP3A2 (500 mg), SP3A3 (16 g), and SP3A4 (12 g). The SP3A2 fraction was subjected to a silica gel CC using CH_2Cl_2/acetone (10/1, v/v), resulting in two fractions, SP3A2A (100 mg) and SP3A2B (120 mg). The SP3A2A fraction was purified on a Sephadex LH-20 CC then on an HPLC system eluting with 60% ACN in water to yield compounds **3** (15 mg, t_R = 26.9 min) and **4** (12 mg, t_R = 15.6 min). The SP3A2B fraction was purified on an HPLC eluting with 60% ACN in water to yield compound **5** (3.4 mg, t_R = 27.1 min).

The SP3A3 fraction (1.0 g) was purified on a Sephadex LH-20 CC using solvent eluent of MeOH/water (9/1, v/v) to obtain fractions SP3A3A (300 mg) and SP3A3B (250 mg). The SP3A3B fraction was then chromatographed on an HPLC system eluting with 22.5% ACN in water to yield compound **1** (20 mg, t_R = 31.1 min). SP3A4 (1.0 g) was purified on a Sephadex LH-20 CC using solvent eluent of MeOH/water (9/1, v/v) to obtain fractions SP3A4A (200 mg) and SP3A4B (180 mg). The SP3A4B fraction was chromatographed on an HPLC eluting with 20% ACN in water to yield compound **2** (15 mg, t_R = 42.0 min).

*Spiruplatoside A (**1**):* White amorphous powder; $[\alpha]_D^{25}$ −64.0 (*c* 0.1, MeOH); m.p. 192°C; HR-ESI-MS *m/z*: 329.0860 $[M-H]^-$ (calcd. for $[C_{14}H_{17}O_9]^-$, 329.0878); ^{1}H-NMR and ^{13}C-NMR (CD_3OD), see Table 1.

*Spiruplatoside B (**2**):* White amorphous powder, $[\alpha]_D^{25}$ −83.0 (*c* 0.1, MeOH); m.p. 216°C; HR-ESI-MS *m/z*: 481.0972 $[M-H]^-$ (calcd. for $[C_{21}H_{21}O_{13}]^-$, 481.0988); ^{1}H-NMR and ^{13}C-NMR (CD_3OD), see Table 1.

Compound **1** was isolated as a white amorphous powder. The HR-ESI-MS of **1** showed a molecular ion peak $[M-H]^-$ at *m/z* 329.0860, confirming the molecular formula of $C_{14}H_{18}O_9$. The ^{1}H-NMR spectrum of **1** showed proton signals of one aromatic proton at δ_H 6.26 (1H, s), one aldehydic proton at δ_H 10.20 (1H, s), one methyl group at δ_H 1.97 (3H, s), and one anomeric proton at δ_H 4.92 (1H, d, J = 7.2 Hz). The ^{13}C-NMR spectrum revealed characteristic resonances of 14 carbons, including one aldehydic carbon at δ_C 193.5, six carbons of benzene ring at δ_C 95.1, 106.2, 106.8, 161.2, 164.1, and 166.1, one methyl carbon directly bonded with aromatic ring at δ_C 6.8, and six carbons assigned to monosaccharide at δ_C 62.5, 71.2, 74.6, 78.0, 78.4, and 102.4. Analysis of ^{1}H- and ^{13}C-NMR data suggested that the chemical structure of **1** was similar to that of eucalmainoside C, a phloroglucinol glucoside from *Eucalyptus maideni* (Tian et al., 2010) except for a shift of the glycosidic linkage position from C-2 to C-6. The HMBC correlations from H-7 (δ_H 10.20) to C-1 (δ_C 106.8)/C-2 (δ_C 164.1)/C-6 (δ_C 161.2) suggested the position of the formyl group at C-1. In addition, the HMBC correlations from H-8 (δ_H 1.97) to C-2 (δ_C 164.1)/C-3 (δ_C 106.2)/C-4 (δ_C 166.1) and from H-5 (δ_H 6.26) to C-1 (δ_C 106.8)/C-3 (δ_C 106.2)/C-4 (δ_C 166.1)/C-6 (δ_C 161.2) indicated positions of the methyl group at C-3 and three oxygenated groups at C-2/C-4/C-6 (Figure 1). Acid hydrolysis of **1** gave a monosaccharide, which was identified as D-glucose by comparing its specific rotation with that of standar D-glucose (The specific rotations ($[\alpha]_D^{25}$) of sugar was determined after dissolving in H_2O for 24h and compared to the literature (lit): D-glucose: found + 48.7 (*c* 0.4, H_2O); lit +48.0) (Abe et al., 1999). The large coupling constant between H-1′ and H-2′ (J = 7.2 Hz) of glucose moiety indicated the monosaccharide as β-D-glucopyranoside. In addition, the position of this sugar at C-6 of phloroglucinol was confirmed by HMBC correlations from H-1′ (δ_H 4.92) to C-6 (δ_C 161.2). Based on the above evidence, the structure of **1** was elucidated as 2,4,6-trihydroxy-3-methylbenzaldehyde 6-*O*-β-D-glucopyranoside, a new compound named spiruplatoside A.

The ^{1}H- and ^{13}C-NMR spectra of **2** exhibited one 2,4,6-trihydroxy-3-methylbenzaldehyde, one monosaccharide, and one galloyl unit (Table 1). NMR data of **2** also showed a small amount of 2-butoxyethanol (Figdore, 1983). The NMR data of **2** were similar to those of spiruplatoside A (**1**) except for the presence of an additional galloyl unit. Moreover, acid hydrolysis of **2** confirmed the sugar as D-glucose. The anomeric coupling constant (J = 7.2 Hz) supported a β-configuration the glucopyranosyl unit. HMBC correlations between H-2″/H-6″ (δ_H 7.09) and C-1″ (δ_C 121.3)/C-3″/C-5″ (δ_C 146.5)/C-4″ (δ_C 139.9)/C-7″ (δ_C 168.3)

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Table 1. NMR data for compounds **1** and **2**

C	Spiruplatoside A (1)		C	Spiruplatoside B (2)	
	δ_C [a,b]	δ_H [a,c] (mult., *J* = Hz)		δ_C [a,b]	δ_H [a,c] (mult., *J* = Hz)
1	106.8	–	1	107.1	–
2	164.1	–	2	164.0	–
3	106.2	–	3	106.5	–
4	166.1	–	4	165.8	–
5	95.1	6.26 (s)	5	95.5	6.23 (s)
6	161.2	–	6	161.0	–
7	193.5	10.20 (s)	7	193.6	10.15 (s)
8	6.8	1.97 (s)	8	6.9	1.97 (s)
6- *O*-Glc			**6- *O*-Glc**		
1′	102.4	4.92 (d, 7.2)	1′	102.6	4.95 (d, 7.2)
2′	74.6	3.50 (m)	2′	74.7	3.55 (t, 7.8)
3′	78.0	3.50 (m)	3′	77.8	3.52 (t, 5.4)
4′	71.2	3.42 (m)	4′	71.1	3.61 (t, 8.4)
5′	78.4	3.45 (m)	5′	75.7	3.71 (m)
6′	62.5	3.75 (dd, 5.4, 12.0) 3.95 (dd, 2.4, 12.0)	6′	64.1	4.52 (dd, 4.8, 12.0) 4.57 (dd, 2.4, 12.0)
			6′- *O*-Gall		
			1″	121.3	–
			2″, 6″	110.3	7.09 (s)
			3″, 5″	146.5	–
			4″	139.9	–
			7″	168.3	–

Note: [a] recorded in CD_3OD, [b] 150 MHz, [c] 600 MHz.

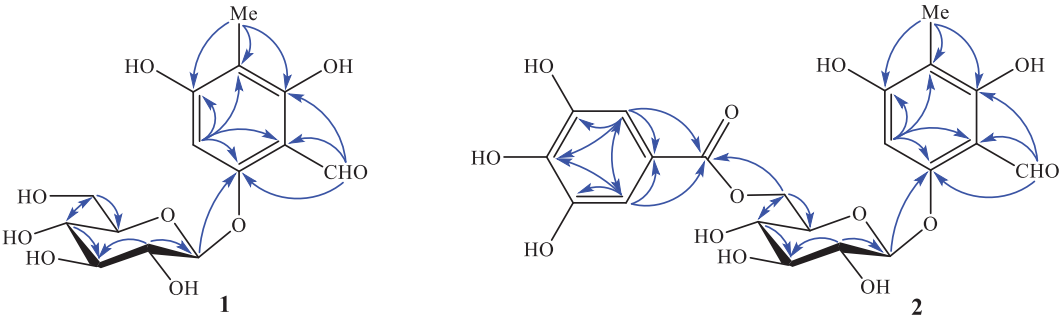

Figure 1. The key HMBC correlations of **1** and **2**

indicated the presence of galloyl unit. In addition, the position of the galloyl at C-6′ of *β*-D-glucopyranosyl unit was further confirmed by HMBC correlation between H-6′ (δ_H 4.52/4.57) and C-7″ (δ_C 168.3). Consequently, compound **2** was elucidated to be 2,4,6-trihydroxy-3-methylbenzaldehyde 6-*O*-(6′-galloyl)-*β*-D-glucopyranoside, a new compound named spiruplatoside B.

The known compounds were determined to be 5,7-dimethoxyflavone (**3**) (Khanapur et al., 2015), 5-hydroxy-7,4′-dimethoxyflavone (**4**) (Solís et al., 2005), 5,7,4′-dimethoxyflavone (**5**) (Smith et al., 2007), terephthalic acid dimethyl ester (**6**) (Liu et al., 2011), terephthalic acid-(2-hydroxyethyl ester)-methyl ester (**7**) (Yasukawa et al., 2016), 13*S*-hydroxy-9*Z*,11*E*-octadecadienoic acid (**8**) (Omar et al., 2003) (Figure 2). Their chemical structures were elucidated by their spectroscopic data and comparing with those reported NMR data in the literature.

Compounds **1**–**8** were evaluated for cytotoxic activity against SK-LU-1 and HepG2 cancer cells (Table 2). Compounds **1** and **2** were the most active, with IC_{50} values ranging from 1.40 to 3.66 μM, comparable to the positive control, ellipticine. Compounds **4** and **5** showed moderate effects with IC_{50} values ranging from 66.09 to 74.46 μM, while the remaining compounds were inactive (IC_{50} > 100 μM). The structure-activity relationship indicates that the galloyl moiety in 2 slightly reduces potency relative to **1**. Consistent with recent reports highlighting the cytotoxicity of phloroglucinol (Lopes-Costa et al., 2017), these findings support phloroglucinol-based scaffolds as potential anticancer leads. The molecular mechanisms underlying the activities of **1** and **2** in cancer cells warrant further investigation.

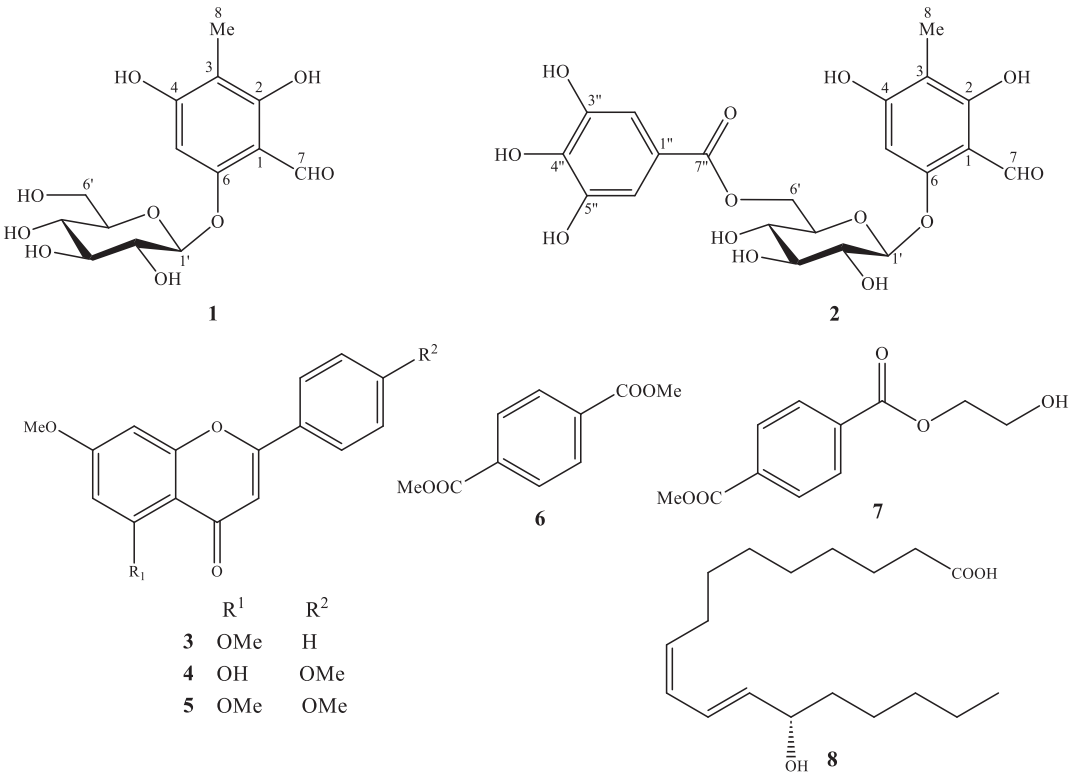

Figure 2. Chemical structures of compounds **1–8**

Table 2. Effects of compounds **1–8** and the Methanol Extract of Microalgae *S. platensis* on the Growth of Human Cancer Cells

Compound	IC_{50} (μM)	
	SK-LU-1	HepG2
1	1.40±0.19	2.42±0.38
2	2.68±0.21	3.66±0.24
3	>100	>100
4	69.05±4.55	74.46±5.27
5	66.09±8.02	69.87±4.87
6	>100	>100
7	>100	>100
8	>100	>100
MeOH extract[a)]	72.07±2.14	92.41±2.08
Ellipticine	3.51±0.38	3.42±0.45

Note: *Ellipticine was used as a positive control.* [a)] *μg/mL.*

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Author Contributions

For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, N.T.M.H. and P.V.K.; methodology, N.T.M.H.; software, B.H.T.; validation, N.Q.A.; formal analysis, H.T.Q., T.H.G.; investigation, V.T.N.L., D.T.T., N.H.P.; resources, N.X.N.; data curation, D.T.T; writing—original draft preparation, N.X.N. and N.T.M.H.; writing—review and editing, D.T.M.H. and N.Q.A.; visualization, B.H.T; supervision, B.H.T.; project administration, N.X.N.; funding acquisition, N.X.N. All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request. Source data are provided with this paper.

Ethics Approval

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.

Conflicts of Interest

The authors declare that they do not have any conflict of interest.

Supporting Information

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