

Steroidal constituents from the seaweed *Sargassum polyporum*

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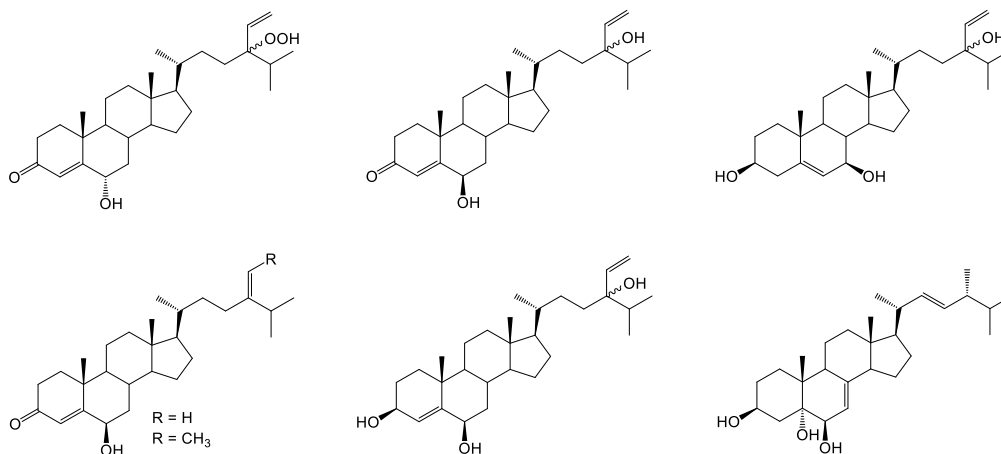
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Abstract

Seven steroids, including one new compound 24 ξ -hydroperoxy-6 α -hydroxy-24-ethylcholesta-4,28(29)-dien-3-one, were isolated from the methanol extract of the brown seaweed *Sargassum polyporum*. Their chemical structures were confirmed by detailed analysis of the 1D, 2D NMR, and HR QTOF mass spectra. Among isolated compounds, 24 ξ -stigmasta-4,28-diene-6 β ,24-diol-3-one and (24 ξ)-stigmasta-4,28-diene-3 β ,6 β ,24-triol exhibited moderate antiproliferative effect against all the five cancer cell lines SK-LU-1 (lung carcinoma), HepG2 (hepatocarcinoma), MCF7 (breast carcinoma), KB (carcinoma in the mouth), and LNCaP (prostate carcinoma).



Keywords: Seaweed, *Sargassum polyporum*, Sargassaceae, steroid, antiproliferative activity

Introduction

Steroids comprise a highly diverse group of metabolically active compounds, all sharing a common carbon skeleton consisting of three six-membered rings fused to one five-membered ring. Steroidal hormones, bile acids, and signaling molecules such as oxysterols are oxygenated derivatives of cholesterol. Oxysterols display a wide range of biological activities with potential physiological, pathological, and pharmacological significance. In addition, they inhibit cell replication and possess cytotoxic properties—effects suggesting that these compounds may play a role in regulating cell proliferation and could serve as promising therapeutic agents against cancer. Owing to the important biological activities of oxysterols, marine organisms have attracted considerable interest compared to terrestrial plants, as they represent a particularly rich and prolific source of these compounds.¹

As a part of our ongoing investigations on steroid derivatives from Vietnamese marine resources,^{2,3} the current paper reveals the isolation and structure elucidation of seven steroids, including one new compound 24 ξ -hydroperoxy-6 α -hydroxy-24-ethylcholesta-4,28(29)-dien-3-one (**1**), from the brown seaweed *Sargassum polyporum*. Their *in vitro* antiproliferative effect against the five human cancer cell lines was also evaluated.

Results and Discussion

Using various chromatographic separations, seven steroids (**1–7**, Fig. S1) were isolated from the methanol extract of the Vietnamese brown seaweed *Sargassum polyporum*. By comparing the 1D and 2D NMR spectroscopic data with those reported, the known steroids were identified as ergosta-6 β -hydroxy-4,24(28)-dien-3-one (**2**),⁴ 6 β -hydroxy-24-ethylcholesta-4,24(28)-dien-3-one (**3**),⁵ 24 ξ -stigmasta-4,28-diene-6 β ,24-diol-3-one (**4**),⁶ (24 ξ)-stigmasta-4,28-diene-3 β ,6 β ,24-triol (**5**),⁶ (24 ξ)-stigmasta-5,28-diene-3 β ,7 β ,24-triol (**6**),⁶ and cerevisterol (**7**).⁷

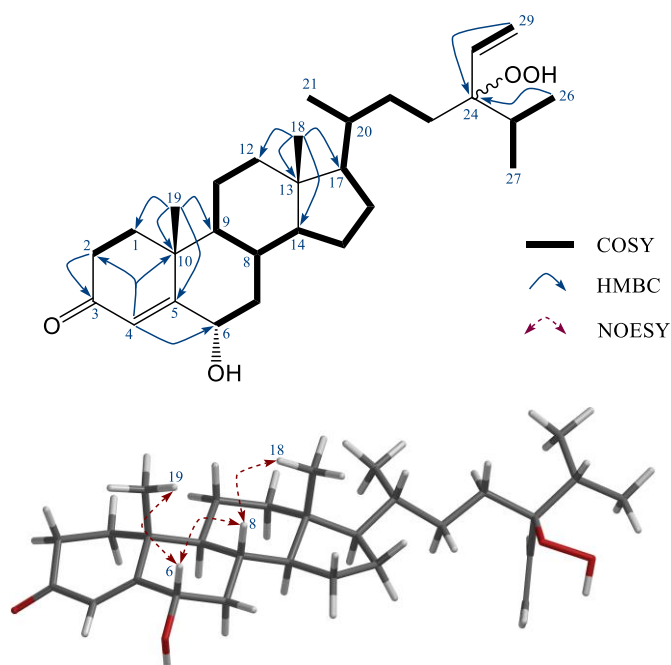


Figure 1. Structure and key COSY, HMBC, and NOESY correlations of **1**.

Table 1. The ^{13}C and ^1H NMR spectral data of **1**

C	$\delta_{\text{C}}^{\text{a,b}}$	$\delta_{\text{H}}^{\text{a,c}}$ mult. (J in Hz)	C	$\delta_{\text{C}}^{\text{a,b}}$	$\delta_{\text{H}}^{\text{a,c}}$ mult. (J in Hz)
1	36.2	1.75 m/2.02 m	16	28.2	1.30 m/1.91 m
2	33.8	2.36 m/2.42 m	17	55.7	1.17 m
3	199.4	-	18	12.0	0.72 s
4	119.7	6.17 d (1.8)	19	18.3	1.18 s
5	171.4	-	20	35.9	1.41 m
6	68.7	4.33 dd (11.4, 5.4)	21	18.8	0.95 d (6.6)
7	41.6	1.05 m/2.17 m	22	28.2	1.52 m/1.62 m
8	34.2	1.60 m	23	28.2	1.52 m/1.62 m
9	53.8	0.92 m	24	89.0	-
10	39.1	-	25	32.0	2.02 m
11	21.1	1.40 m/1.53 m	26	16.6	0.89 ^d
12	39.4	1.18 m/2.02 m	27	17.7	0.87 ^d
13	42.5	-	28	137.1	5.74 ddd (18.0, 11.4, 2.4)
14	55.6	1.08 m	29	116.4	5.15 br d (18.0) 5.27 ddd (11.4, 3.0, 1.2)
15	24.2	1.14 m/1.62 m	OOH	-	7.02 s 7.03 s

^aRecorded in CDCl_3 ; ^b150 MHz; ^c600 MHz; ^dOverlapped coupling signals (Fig. S3 and S11). All assignments were done by HSQC, HMBC, ^1H - ^1H COSY, and NOESY experiments

Compound **1** was isolated as a white solid. Its molecular formula, $\text{C}_{29}\text{H}_{46}\text{O}_4$, was determined by HR-QTOF-MS with the quasi-molecular ion peak at m/z 459.3468 $[\text{M}+\text{H}]^+$. Its ^{13}C and ^1H NMR spectral data are indicative of a steroid from the brown seaweed genus *Sargassum*.⁸ Comparison of the ^{13}C and ^1H NMR spectral data of **1** with those of **2–4** suggested the occurrence of the 6-hydroxy-4-ene-3-one steroid core, containing typical signals of one ketone [δ_{C} 199.4 (C-3)], one trisubstituted double bond [δ_{C} 119.7 (C-4) and 171.4 (C-5)/ δ_{H} 6.17 (1H, d, $J = 1.8$ Hz, H-4)], one oxymethine [δ_{C} 68.7 (C-6)/ δ_{H} 4.33 (1H, dd, $J = 11.4, 5.4$ Hz, H-6)], and two singlet methyls [δ_{C} 12.0 (C-18) and 18.3 (C-19)/ δ_{H} 0.72 (H-18) and 1.18 (H-19), each 3H, s]. This was confirmed by detailed analysis of the HSQC, HMBC, COSY, and NOESY correlations (Fig. 1). However, the ^{13}C NMR spectral data at C-3 (δ_{C} 199.4), C-4 (δ_{C} 119.7), C-5 (δ_{C} 171.4), C-6 (δ_{C} 68.7), C-7 (δ_{C} 41.6), and C-8 (δ_{C} 34.2) of **1** were too different from those of **2–4** and 24 ξ -hydroperoxy-6 β -hydroxy-24-ethylcholesta-4,28(29)-dien-3-one at δ_{C} 200.5 (C-3), 126.3 (C-4), 168.5 (C-5), 73.3 (C-6), 38.6 (C-7), 29.7 (C-8),⁵ indicating the α -orientation of the 6-OH group in **1**. The β -orientation of H-6 was further supported by an agreement of the ^{13}C NMR spectral data at C-3 to C-8 of **1** with those of ergosta-6 α -hydroxy-4,24(28)-dien-3-one at δ_{C} 199.79 (C-3), 120.07 (C-4), 171.77 (C-5), 69.09 (C-6), 41.91 (C-7), 34.20 (C-8)⁴ and strong NOESY correlations (Fig. 1) of H-6 (δ_{H} 4.33) with H-8 (δ_{H} 1.60) and H-19 (δ_{H} 1.18). An agreement of the ^{13}C NMR spectral data for the side chain of **1** with those of 24 ξ -hydroperoxy-6 β -hydroxy-24-ethylcholesta-4,28(29)-dien-3-one⁵ in combination with detailed analysis of the HSQC, HMBC, and COSY correlations (Fig. 1) clearly confirmed the presence of the hydroperoxy group at C-24 and the terminal double bond C-28/C-29. The hydroperoxyl proton signal appeared as two singlets at δ_{H} 7.02 and 7.03 ppm,⁵ while H-26 and H-27 appeared as overlapped coupling signals (Fig. S3 and S11), suggesting that **1** was likely a mixture of the 24*R* and 24*S* epimers.⁵ However, many attempts to separate the two isomers by

normal and reversed-phase HPLC were unsuccessful. Thus, **1** was elucidated as 24 ξ -hydroperoxy-6 α -hydroxy-24-ethylcholesta-4,28(29)-dien-3-one.

Table 2. Antiproliferative activity of **2–7** against five human cancer cell lines

Comp.	IC ₅₀ values (μ M)				
	SK-LU-1	HepG2	MCF7	KB	LNCaP
2	> 100	> 100	> 100	> 100	> 100
3	> 100	> 100	> 100	> 100	> 100
4	38.76 $\pm$ 2.70	36.10 $\pm$ 2.29	41.93 $\pm$ 1.24	41.26 $\pm$ 2.93	45.69 $\pm$ 2.59
5	46.08 $\pm$ 2.99	40.69 $\pm$ 2.98	53.72 $\pm$ 1.71	38.34 $\pm$ 3.24	43.41 $\pm$ 2.86
6	96.81 $\pm$ 4.41	92.19 $\pm$ 6.55	97.81 $\pm$ 6.15	95.70 $\pm$ 7.20	99.09 $\pm$ 5.69
7	> 100	> 100	> 100	> 100	> 100
Ellip. ^a	1.58 $\pm$ 0.16	1.34 $\pm$ 0.08	1.46 $\pm$ 0.08	1.34 $\pm$ 0.12	1.42 $\pm$ 0.08

^aEllipticine was used as positive control; Results are the means $\pm$ standard deviation (S.D.) of triplicate experiments.

Compounds **2–7** were evaluated for their *in vitro* antiproliferative activity against five human cancer cell lines SK-LU-1 (lung carcinoma), HepG2 (hepatocarcinoma), MCF7 (breast carcinoma), KB (carcinoma in the mouth), and LNCaP (prostate carcinoma) using the MTT assay,⁹ with the previously reported steps² (Compound **1** could not be evaluated due to its insufficient quantity after numerous attempts to separate two isomers by normal-phase and reversed-phase HPLC). As the results (Table 2), 24 ξ -stigmasta-4,28-diene-6 β ,24-diol-3-one (**4**) and (24 ξ)-stigmasta-4,28-diene-3 β ,6 β ,24-triol (**5**) exhibited moderate effect against all the five cancer cell lines with IC₅₀ values ranging from 36.10 to 53.72 μ M, relative to that of the positive control ellipticine with IC₅₀ values ranging from 1.34 to 1.58 μ M. (24 ξ)-stigmasta-5,28-diene-3 β ,7 β ,24-triol (**6**) revealed weak activity on these cell lines with IC₅₀ values ranging from 92.19 to 99.09 μ M, while ergosta-6 β -hydroxy-4,24(28)-dien-3-one (**2**), 6 β -hydroxy-24-ethylcholesta-4,24(28)-dien-3-one (**3**), and cerevisterol (**7**) were less active with IC₅₀ > 100 μ M. Comparison of the structures **2–7** suggested that the presence of the hydroxy group at C-24 might play an important role for their antiproliferative effect against the tested cancer cell lines.

Conclusions

In summary, seven steroids, including one new compound, 24 ξ -hydroperoxy-6 α -hydroxy-24-ethylcholesta-4,28(29)-dien-3-one (**1**), were isolated from the Vietnamese brown seaweed *Sargassum polyporum*. Their structures were characterised by 2D and 1D NMR as well as HR-QTOF-MS experiments. In addition, moderate antiproliferative effect against all the five tested cancer cell lines SK-LU-1 (lung carcinoma), HepG2 (hepatocarcinoma), MCF7 (breast carcinoma), KB (carcinoma in the mouth), and LNCaP (prostate carcinoma) was observed for 24 ξ -stigmasta-4,28-diene-6 β ,24-diol-3-one (**4**) and (24 ξ)-stigmasta-4,28-diene-3 β ,6 β ,24-triol (**5**) with IC₅₀ values ranging from 36.10 to 53.72 μ M.

Experimental Section

General experimental procedures. Optical rotations were obtained on a JASCO P-2000 polarimeter (Tokyo, Japan). Circular dichroism (CD) spectra were recorded with an Chirascan spectropolarimeter (Applied Photophysics, Leatherhead, UK). High resolution quadrupole time-of-flight mass spectra were recorded on an Agilent 6530 Accurate-Mass spectrometer (CA, USA). The ^1H NMR and ^{13}C NMR spectra were obtained on AVANCE III HD 500 and NEO 600 FT-NMR spectrometers (Bruker, Karlsruhe, Germany) with TMS as an internal standard. High performance liquid chromatography (HPLC) was performed on an Agilent 1260 Infinity II system (Agilent Technologies, USA) equipped with a G7112B Binary Pump, a G7115A diode array detector, and a G7129A auto-sampler. Column chromatography (CC) was carried out on Diaion HP-20 (Supelco, Bellefonte, PA, USA), silica gel (Kieselgel 60, 70–230 mesh and 230–400 mesh, Merck, Darmstadt, Germany), and reversed-phase silica gel (ODS-A, 12 nm S-150 μm , YMC, Kyoto, Japan) resins. Pre-coated silica gel 60 F₂₅₄ (1.05554.0001, Merck, Darmstadt, Germany) and RP-18 F_{254S} plates (1.15685.0001, Merck) were used for TLC and spots were visualized by spraying with aqueous 10% H_2SO_4 , followed by heating for 3–5 min.

Seaweed material. The seaweed *Sargassum polyporum* Montagne 1842 samples were collected at Ly Son, Quang Ngai, Vietnam, in December 2024. The species was identified by Prof. Do Cong Thung (Institute of Science and Technology for Energy and Environment, VAST). A voucher specimen (No: DLB-2024-LS.01) is kept at the Institute of Chemistry, VAST, Hanoi, Vietnam.

Extraction and isolation. The dried seaweed *Sargassum polyporum* (5 kg) was desalted and extracted three times with methanol at room temperature, yielding a MeOH residue (M, 60 g). Residue M (60 g) was separated on reversed-phase silica gel CC, eluting with acetone– H_2O (3:1, v/v) to afford 10 fractions, M1–M10. Fractions M5 (2.0 g) and M6 (1.5 g) were combined and separated into five subfractions, M5A–M5E, using reversed phase silica gel CC with acetone– H_2O (3:1, v/v). Subfraction M5E (0.2 g) was further separated on silica gel CC with *n*-hexane–EtOAc (4:1, v/v) to give three smaller fractions M5E1–M5E3. Fraction M5E2 (30 mg) was purified by HPLC with mobile phase of ACN– H_2O (9:1, v/v) to obtain compounds **2** (1.2 mg) and **3** (17 mg). Fractions M7 (5.5 g) and M8 (7.5 g) were combined and separated into four subfractions, M7A–M7D, using reversed phase silica gel CC with acetone– H_2O (3:1, v/v). Fraction M7A (3 g) was further separated on reversed phase silica gel CC with acetone– H_2O (3:1, v/v) yielding four subfractions, M7A1–M7A4. Subfraction M7A3 (300 mg) was separated into three smaller fractions, M7A3A–M7A3C, using reversed phase silica gel CC with acetone– H_2O (2:1, v/v). Compound **6** (0.7 mg) was purified from M7A3C (18 mg) after subjecting it to silica gel CC with *n*-hexane–EtOAc (2:1, v/v). Fraction M7B (3 g) was treated by the same manner as done for M7A giving eight subfractions, M7B1–M7B8. Subfraction M7B3 (70 mg) was further separated on reversed phase silica gel CC with MeOH– H_2O (8:1, v/v) and then on silica gel CC with *n*-hexane–EtOAc (3:1, v/v) to get compound **4** (4.0 mg). Compound **5** (2.5 mg) was purified from M7B7 (50 mg) after subjecting it to reversed phase silica gel CC with MeOH– H_2O (8:1, v/v). Subfraction M7B8 (400 mg) was further separated on reversed phase silica gel CC with MeOH– H_2O (8:1, v/v) and then on silica gel CC with *n*-hexane–EtOAc (1:1.5, v/v) to obtain compound **7** (1.0 mg). Fraction M7C (2.5 g) was separated into five subfractions, M7C1–M7C5, using silica gel CC with *n*-hexane–EtOAc (3:1, v/v). Purification of M7C2 (90 mg) was achieved on reversed phase silica gel CC with MeOH– H_2O (10:1, v/v) and then on HPLC with mobile phase of ACN– H_2O (6:4, v/v) to give **1** (0.6 mg).

24 ξ -hydroperoxy-6 α -hydroxy-24-ethylcholesta-4,24(28)-dien-3-one (1). White solid; $[\alpha]_{\text{D}}^{20}$ 31.7 (*c* 0.03, MeOH); CD (MeOH) λ_{max} (mdeg): 321 (–5.2), 243 (+26.2), and 204 (+24.6) nm; ^1H (CDCl_3 , 600 MHz) and ^{13}C

NMR (CDCl₃, 150 MHz) spectral data, see Table 1; HR-QTOF-MS: *m/z* 459.3468 [M+H]⁺ (calcd for C₂₉H₄₇O₄⁺, 459.3469).

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Supplementary Material

Supplementary data associated with this article are available in the Electronic Supplementary Material (ESI).

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