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RESEARCH PAPER

Anti-inflammatory Effects of Sargachromanol I, Sargachromanol G, and Saringosterol from Hexane Fraction of *Myagropsis myagroides*

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Abstract The anti-inflammatory activity of benzopyran derivatives extracted from the *Myagropsis myagroides* against lipopolysaccharide (LPS)-induced RAW 264.7 murine macrophage cell line was examined. The three constituents of *M. myagroides* extracts were identified as the sargachromanol G, sargachromanol I, and saringosterol by ^{1}H and ^{13}C NMR. Sargachromanol G, sargachromanol I, and saringosterol at concentrations of 50 μg/mL showed inhibitory effects on LPS induced interleukin-6 production (by 84%, 90%, and 96%, respectively) and tumor necrosis factor (by 74%, 82%, and 98%, respectively). These results confirm the potential anti-inflammatory effects of sargachromanol G, sargachromanol I, and saringosterol.

Keywords: anti-inflammatory effect, *Myagropsis myagroides*, sargachromanol G, sargachromanol I, saringosterol

1. Introduction

Inflammatory diseases have recently been exposed to various harmful factors due to industrialization and urbanization, and are increasing in various age groups. To solve this problem, the synthetic anti-inflammatory drugs currently used temporarily alleviate symptoms, but when used excessively, severe side effects such as gastric ulcers, gastritis, and cardiovascular diseases occur. New natural product-derived anti-inflammatory pharmaceuticals are needed to treat inflammatory diseases such as cancer, neurological diseases, metabolic disorders, and cardiovascular diseases [1]. Therefore, studies are being conducted to develop a therapeutic agent having low toxicity using various natural products and food extracts.

Marine macroalgae have been used as part of a healthy diet in East Asia for centuries. *Myagropsis myagroides* is a brown algae that is extensively distributed along the coast of Korea, Japan, and China [2]. *M. myagroides* has biological activity with reported hepatoprotective effect [3], anti-inflammatory activity [2,4], antimicrobial activity [5], anti-atopic activity [6], angiotensin-I converting enzyme inhibitory activity [7], and anticoagulant activity [8]. The anti-inflammatory activity of 6,6'-bieckol, phlorofucofuroeckol b, and fucoxanthin isolated from *M. myagroides* was previously reported [2,9,10]. *M. myagroides* belongs to the *Sargassaceae* family, and many researchers have previously isolated benzopyran derivaties from *Sargassaceae* species. Previous studies determined the benzopyran structures of sargachromanol A to P extracted from *Sargassum siliquastrum* [11]. In addition, the anti-inflammatory effects of sargachromanol D [12], sargachromenol [13], and mojabanchromanol b [2] isolated from *M. myagroides* extracts were reported. Saringosterol has been found in *S. ringgoldiamm*, *Spiraea thunbergii*, *S. fusiforme,* and *Lessonia nigrescens* [14], and has antitubercular [15], antiatherosclerotic [16], and lipase inhibitory activities [13].

No previous study has been reported to show the anti-inflammatory activity of sargachromanol I and saringosterol. Therefore, we have isolated benzopyran derivaties such as sargachromanol G, sargachromanol I, and saringosterol from *M. myagroides* for the first time.

In addition, pro-inflammatory cytokines secretion inhibitory effect of three compounds isolated from *M. myagroides*

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extracts was confirmed, suggesting their anti-inflammatory activity potential.

2. Materials and Methods

2.1. Chemicals and reagents

NMR spectra were measured in $CDCl_3$ solution, and were recorded on JNM-ECA600 (JEOL Ltd, Tokyo, Japan) using TMS as an internal standard. Chemical shifts (δ) were expressed in ppm with reference to the solvent signals. Column chromatography was performed using flash silica gel (70–230 mesh, Merck Art. Darmstadt, Germany, 5 × 10 cm column,) and silica gel (10 × 12 cm column), preparative TLC silica gel plates (N0. 5744, Merck, Germany), and Sephadex LH-20 gel (Amersham pharmacia Biotech AB, Uppsala, Sweden, 2.5 × 90 cm column). LPS, dimethylsulfoxide (DMSO), and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were purchased from Sigma (St. Louis, MO, USA). Enzyme-linked immunosorbent assay (ELISA) kits for TNF-α and IL-6 were purchased from BD Biosciences (San Diego, CA, USA), and Dulbecco's Modified Eagle's Medium (DMEM) was purchased from GIBCO (Grand Island, Nebraska, USA). Fetal bovine serum (FBS) and penicillin/streptomycin were purchased from Hyclone (Logan, Utah, USA).

2.2. Seaweed

M. myagroides collected from Song-Jeong, Busan, Korea in March 2011 was used in this study. This species was collected from the subtidal zone at Gijang of Busan. A voucher specimen (MGARBa000087) has been deposited at the Marine Green Algal Resources Bank.

2.3. Extraction and purification of active compounds

Powdered *M. myagroides* (1.5 kg) was extracted with 70% methanol for 24 h at room temperature with an agitator (H-0820, Dongwon Science Co., Busan, Korea). The extract was then centrifuged at 3,000 rpm for 10 min, and the supernatant was filtered and concentrated using a rotary evaporator (RE200, Yamato Co., Tokyo, Japan). The residue extraction step was repeated twice in the same way.

The concentrated methanol extract (85 g) was sequentially partitioned into *n*-hexane, chloroform, ethyl acetate, butanol, and water. Each solvent fraction was evaluated for anti-inflammatory activity by enzyme-linked immunosorbent assay.

The active n-hexane fraction (13 g) of *M. myagroides* was separated by silica gel flash column chromatography (CHCl3: MeOH, 100: 1-1: 1, v / v). And then the fractions eluted with CHCl3: MeOH = 50: 1, v/v was purified by sephadex LH-20 column chromatography ($CHCl_3$: MeOH, 1: 1, v/v), and 2 fractions obtained (Fr. 1 and Fr. 2). Fr. 2 (1.2 g) was separated into 5 fractions (Fr. 3 to Fr. 7) by an octadecyl silica (ODS) Sepak cartridge (60-90% methanol). Fr. 4 (242 mg) was successively rechromatographed on a sephadex LH-20 column chromatography (methanol) and ODS Sepak cartridge (50-60% methanol) to isolated the 6 fractions (Fr. 4-1 to Fr. 4-6). Finally, Fr. 4-1 and Fr. 4-2 were separated using preparative ODS HPLC (75% methanol, 9 mL/min) to yield Mm-1 (20 mg) and Mm-2 (52 mg), respectively. Fr. 6 (30.9 mg) was analyzed by thin-layer chromatography (silica gel), and the potent active principle, Mm-4 (3 mg), was isolated. The three compounds were identified using ^{1}H and ^{13}C NMR.

2.4. Enzyme-linked immunosorbent assay

IL-6 concentrations were determined using an ELISA kit (BD Bioscience, San Diego, CA, USA). Briefly, Raw 264.7 cells (2.5×10^5 cells/mL) were stimulated in 24-well plates with LPS (1 μg/mL) and incubated with the indicated concentration of extracts (50 and 100 μg/mL) for 24 h. Levels of TNF-α and IL-6 in the culture medium were then measured by ELISA using anti-mouse TNF-α and IL-6 antibodies and a biotinylated secondary antibody according to the manufacturer's instructions.

2.5. Statistical tests

Data are expressed as mean ± standard deviation. Statistical evaluation was carried out by analysis of variance and Student's *t*-test with SAS software (SAS Institute, Inc., Cary, NC, USA), with $p < 0.05$ as the level of significance.

3. Results and Discussion

3.1. Purification of active compounds

To identify active compounds with anti-inflammatory activity, the methanol extract was fractionated into polar and non-polar layers. Treatment of RAW 264.7 cells with lipopolysaccharide (LPS) alone resulted in a significant increase in the production of the pro-inflammatory cytokines IL-6 and TNF-α (Fig. 1). However, methanol extract and its fractions reduced the production of IL-6 and TNF-α significantly. The inhibition abilities of the hexane and chloroform fractions were similar to that of the methanol extract. The ethyl acetate, butanol, and water fractions resulted in significantly higher production of IL-6 and TNF-α compared to that reported for the methanol extract. The isolation of active compounds from the chloroform fraction did not progress because of low yield.

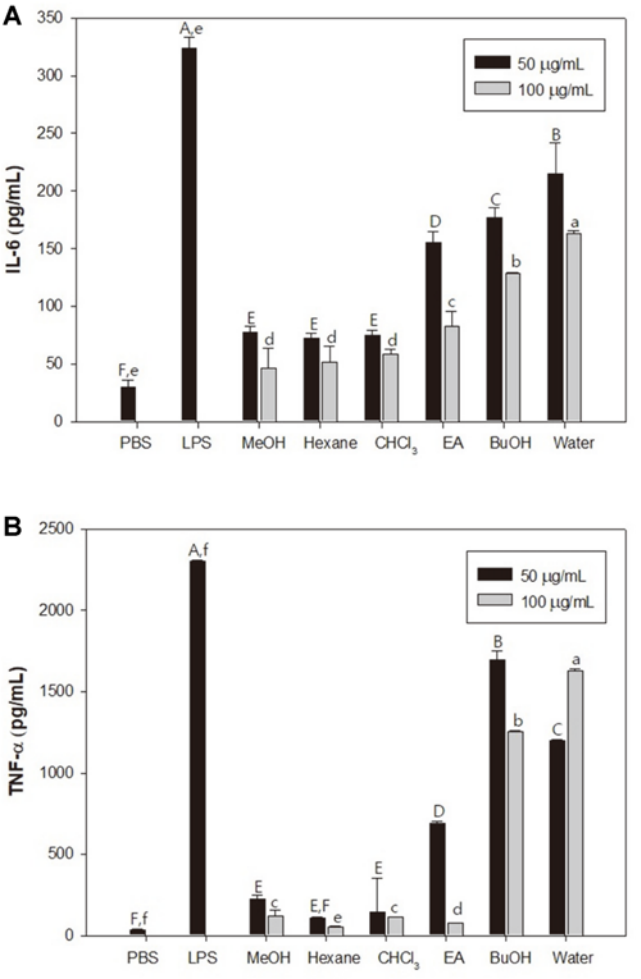

Fig. 1. Inhibitory effect of solvent fractions from *Myagropsis myagroides* on the production of IL-6 (A) and TNF-α (B) in lipopolysaccharide (LPS)-stimulated RAW 246.7 cells. Values are the mean ± S.D. of triplicate experiments ($p < 0.05$).

The Fractions with the cytokine inhibitory activity of the *M. myagroides* extract provided three components identified by chromatography, spectroscopic analysis, and published data [17]. The three constituents were characterized as sargachromanol I, sargachromanol G, and saringosterol (Fig. 2). Sargachromanol G contained two ring systems, one carbonyl group at C-9', and 6 C = C double bonds but sargachromanol I contained 5 C = C double bond [11]. Sargachromanol G and sargachromanol I similar with mojabanchromanol b, isolated from *M. myagroides* extract but differ in the carbonyl group of *M. myagroides* located at C-10' [2]. The anti-inflammatory compounds sargachromanol G, sargachromanol I, and saringosterol were isolated from *M. myagroides* for the first time in this study.

Sargachromanol I: NMR data were reported by previously study [2,17] (Table 1).

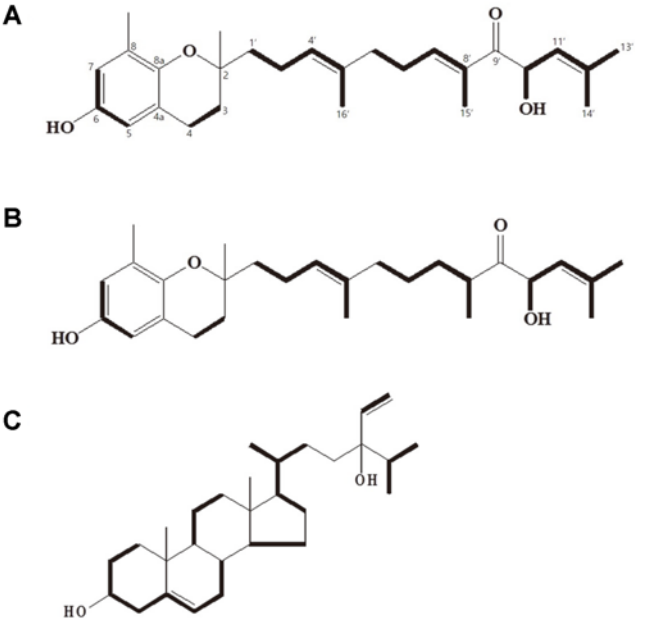

Fig. 2. Structure of sargachromanol G (A), sargachromanol I (B), and saringosterol (C) isolated from *Myagropsis myagroides*.

Sargachromanol G: ^{1}H NMR (600 MHz, $CDCl_3$) 6.37 (1H, d, 1.4 Hz), 5.27 (1H, dd, 9.7, 6.2 Hz), 6.47 (1H, d, 2.8 Hz), 5.12 (1H, br t, 6.5 Hz), 4.97 (1H, br d, 9.6 Hz), 4.76 (1H, s), 4.04 (1H, d, 6.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) 75.1, 31.4, 22.4, 121.1, 112.6, 147.9, 115.7, 127.2, 145.8, 39.4, 22.0, 125.6, 133.5, 38.0, 27.4, 145.4, 133.7, 201.3, 69.8, 123.4, 137.9, 25.8, 18.3, 11.7, 15.7, 24.0, 16.0 (Table 1) [2].

Saringosterol: ^{1}H NMR (600 MHz, $CDCl_3$) 5.72 (1H, m, 4.2 Hz), 5.34 (1H, brs, 2.4 Hz), 5.26 (1H, dd, 1.8Hz, 4.2 Hz), 5.14 (1H, dd, 1.2 Hz, 18 Hz), 3.51 (1H, m, 5.5 Hz), 0.99 (3H, s), 0.95 (3H, d, 6.6 Hz), 0.87 (3H, d, 3.6 Hz), 0.86 (3H, d, 3 Hz), 0.67 (3H, s), ^{13}C NMR (150 MHz, $CDCl_3$) 37.2, 31.6, 71.8, 42.3, 140.7, 121.7, 31.9, 31.9, 50.1, 19.4, 21.0, 39.7, 42.2, 56.7, 24.3, 28.3, 36.2, 11.8, 19.4, 36.2, 18.9, 28.2, 28.5, 89.1, 31.9, 16.7, 17.7, 137.2, 116.3 (Table 1).

3.2. Effects of three benzopyran derivaties on LPS-induced pro-inflammatory cytokines production

Tumor necrosis factor (TNF)-α and interleukin (IL)-6 play important roles in inflammatory diseases [18], and TNF-α particularly so in the continuation and progress of acute and chronic inflammation [19]. The regulation of TNF-α could therefore be of great therapeutic potential. In addition, IL-6 is one of the typical pro-inflammatory cytokines, and its overproduction causes the growth of tumors or autoimmune diseases [20].

Table 1. NMR spectral data of sargachromanol G, sargachromanol I, and saringosterol [2,17]

C/H#	Sargachromanol G		Sargachromanol I		C/H#	Saringosterol	
	δ_C	δ_H	δ_C	δ_H		δ_C	δ_H
2	75.1		75		1	37.2	1.83, 1.07
3	31.4	1.78 m, 1.71 m	31.3	1.78 m,1.73 m	2	31.6	1.83, 1.52
4	22.4	2.68 t	22.4	2.68 t	3	71.8	3.51 d
4a	121.1		121.1		4	42.3	2.22, 2.27
5	112.6	6.37 d	112.6	6.37 d	5	140.7	
6	147.9		147.9		6	121.7	5.34 s
7	115.7	6.47 d	115.6	6.47 d	7	31.9	1.51, 1.95
8	127.2		127.1		8	31.9	1.48
8a	145.8		145.7		9	50.1	
1’	39.4	1.62 m, 1.51 m	39.5	1.63 m, 1.52 m	10	19.4	
2’	22.0	2.11s	22.1	2.10 s	11	21.0	1.42, 1.48
3’	125.6	5.12 br t	124.8	5.11 br t	12	39.7	1.99, 1.14
4’	133.5		134.3		13	42.2	
5’	38.0	2.08d	39.4	1.92 s	14	56.7	0.98
6’	27.4	2.33d	25.2	1.36 m, 1.33 m	15	24.3	1.58 m, 1.06 m
7’	145.4	6.54 br t	33.4	1.56 m, 1.32m	16	28.3	1.4-1.5
8’	133.7		41.2	2.68 m	17	36.2	1.12
9’	201.3		214.6		18	11.8	0.67s
10’	69.8	5.27 dd	74.3	4.87 dd	19	19.4	0.99s
11’	123.4	4.97 br d	120.9	4.97 br d	20	36.2	1.39
12’	137.9		140.0		21	18.9	0.95
13’	25.8	1.72d	25.9	1.79s	22	28.2	1.86 m, 1.27 m
14’	18.3	1.81s	18.6	1.84s	23	28.5	1.75 m, 1.62 m
15’	11.7	1.79s	16.0	1.05s	24	89.1	
16’	15.7	1.58s	15.6	1.55 s	25	31.9	2.02
17’	24.0	1.25s	24.0	1.25 s	26	16.7	0.87
18’	16.0	2.11s	16.0	2.11 s	27	17.7	0.86
					28	137.2	5.72 t
					29	116.3	5.26 m, 5.14 m

Three active compounds, sargachromanol G, sargachromanol I, and saringosterol, were isolated from the hexane fraction of *M. myagroides* methanol extract. Sargachromanol G, sargachromanol I, and saringosterol used at a concentration of 50 μg/mL significantly inhibited the production of IL-6 (by 84%, 90%, and 96%, respectively) and TNF-α (by 74%, 82%, and 98%, respectively) (Fig. 3).

Seaweed contains phytochemicals such as carotenoids, phycobilins, fatty acids, polysaccharides, vitamins, sterols, tocopherols, and polyphenols, which have various physiological properties [21]. The anti-inflammatory activity of bioactive compounds including benzopyrans and phytosterols has previously been reported [22,23]. In our previous study, mojabanchromanol b from *M. myagroides* was shown to have marked anti-inflammatory effects through the inhibition of nitric oxide (NO) and pro-inflammatory cytokine production [2]. In addition, sargachromanol I from *M. myagroides* inhibited amylase activity [17], and its free radical scavenging activity and anticollagenase properties were confirmed [24]. The anti-inflammatory effects of sargachromanol G isolated from *Sargassum siliquastrum* have been reported by Yun *et al.* [25]. It has been reported that the anti-inflammatory activity of sargachromanol G results from the modulation of pro-inflammatory cytokines and mediators through inhibition of NF-kB activation and MAPK phosphorylation [25]. Similarly, in this study we have confirmed the inhibition of pre-inflammatory cytokine secretion of sargachromanol G isolated from *M. myagroides* extracts. However, further studies are needed to identify anti-inflammatory mechanisms related to NF-kB activation and MAPK phosphorylation.

In this study, the first reported inhibition of pro-inflammatory cytokines by sargachromanol G, sargachromanol I, and saringosterol isolated from *M. myagroides*. As seen above, sargachromanol G, sargachromanol I, and saringosterol from *M. myagroides* have anti-inflammatory effects, and this confirms their potential as anti-inflammatory agents.

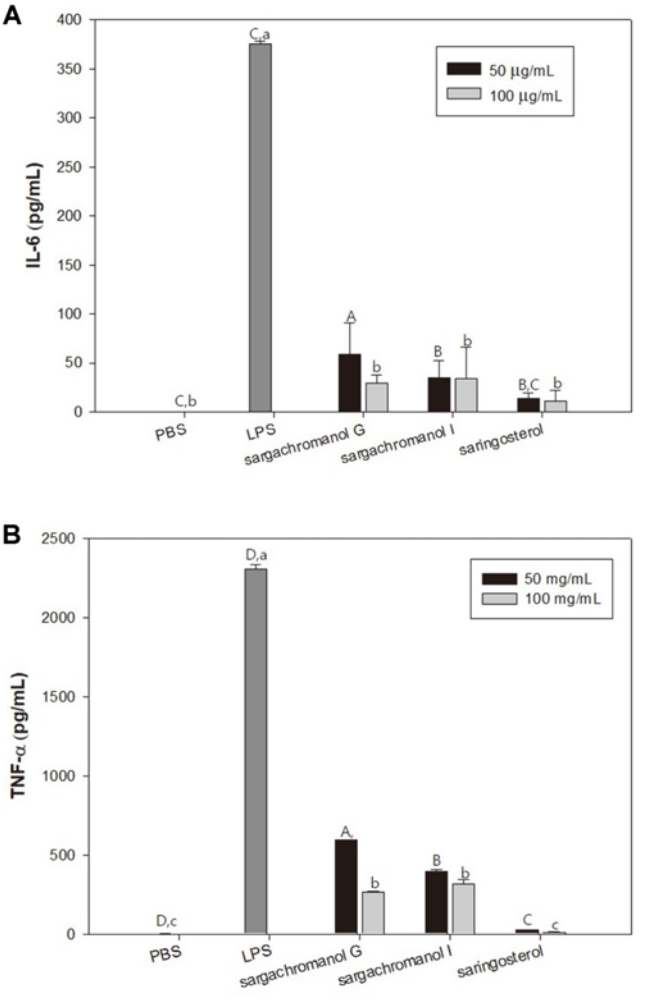

Fig. 3. Inhibitory effect of sargachromanol G, sargachromanol I, and saringosterol from *Myagropsis myagroides* on the production of IL-6 (A) and TNF-α (B) in lipopolysaccharide (LPS)-stimulated RAW 246.7 cells. Values are the mean ± S.D. of triplicate experiments ($p < 0.05$).

4. Conclusion

In conclusion, the anti-inflammatory compounds sargachromanol G, sargachromanol I, and saringosterol were isolated from *M. myagroides* extracts for the first time in this study. In addition, we identified sargachromanol I and saringosterol as novel anti-inflammatory substances for the first time. The results from this study showed that sargachromanol G, sargachromanol I, and saringosterol significantly reduced the production of the pro-inflammatory cytokines IL-6 and TNF-α. Therefore, further studies on the anti-inflammatory mechanisms of sargachromanol G, sargachromanol I, and saringosterol are needed, and it is considered important to identify potential anti-inflammatory effects of these compounds.

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The authors declare no conflict of interest.
Neither ethical approval nor informed consent was required for this study.

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