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Antioxidant, anti-inflammatory, and antibacterial activities of a 70% ethanol-*Symphyocladia linearis* extract

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Abstract

Research on the potential biological activity of red alga *Symphyocladia* spp. has been limited to *Symphyocladia latiuscula*, which is widely used as a food ingredient in Korea. Here, we examined the biological activity of another species, *Symphyocladia linearis*, which is found in Korea and was reported as a new species in 2013. The aim of this study was to evaluate the antioxidant, anti-inflammatory, and antibacterial properties of a 70% ethanol extract of *S. linearis*. Antioxidant activity, which was evaluated using radical scavenging assays, revealed half maximal inhibitory concentration values for 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH) and 2,2′-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS) of 34.57 and 11.70 μg/mL algal extract, respectively. Anti-inflammatory activity of the *S. linearis* ethanolic extract was evaluated using RAW 264.7 cells by measuring the inhibition of lipopolysaccharide-induced nitric oxide (NO) and prostaglandin E_2 (PGE_2) production. The potential cytotoxicity of NO and PGE_2 was first examined, confirming no toxicity at concentrations ranging from 10–100 μg/mL. NO production was inhibited 61.1% and 78.0% at 50 and 100 μg/mL *S. linearis* extract, respectively; and PGE_2 production was inhibited 69.1%, 83.2%, and 94.8% at 25, 50, and 100 μg/mL *S. linearis* extract, respectively. Thus, the *S. linearis* extract showed very strong efficacy against PGE_2 production. The cellular production of reactive oxygen species, measured using 2′,7′-dichlorofluorescin diacetate fluorescence, was inhibited 48.8% by the addition of 100 μg/mL *S. linearis* extract. Antibacterial activity was evaluated using the disc diffusion method and minimum inhibitory concentration (MIC). *S. linearis* was effective only against gram-positive bacteria, exhibiting antibacterial activity against *Staphylococcus aureus* with a MIC of 256 μg/mL extract and against *Bacillus cereus* with a MIC of 1,024 μg/mL extract. Based on these results, we infer that a 70% ethanolic extract of *S. linearis* possesses strong anti-inflammatory properties, and therefore has the potential to be used in the prevention and treatment of inflammatory and immune diseases.

Keywords: Anti-inflammatory, Antioxidant, Antibacterial, *Symphyocladia linearis*

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Introduction

The genus *Symphyocladia* belongs to the family Rhodomelaceae and comprises several species of red algae. Seven *Symphyocladia* species (*Symphyocladia linearis*, *Symphyocladia marchantioides*, *Symphyocladia glabra*, *Symphyocladia pumila*, *Symphyocladia lithophila*, *Symphyocladia jejuinsula*, and *Symphyocladia latiuscula*) are known to inhabit Korean coasts (Kang & Kim, 2013). Among the seven species, *S. latiuscula* has been extensively studied for various biological activities, including anti-tyrosinase (Paudel et al., 2019c), anti-Alzheimer's (Paudel et al., 2019b), anti-diabetic (Paudel et al., 2019a), antifungal (Xu et al., 2014), antiviral (Park et al., 2005), antioxidative (Zhang et al., 2007), and anti-aldose reductase activity (Wang et al., 2005). In addition, *S. latiuscula* has been registered as a food ingredient in Korea (Ministry of Food and Drug Safety) and is widely used industrially.

When subjected to environment stress (e.g., UV light, air pollution, ionizing radiation, smoke), reactive oxygen species (ROS) are generated, such as hydroxyl, superoxide, and lipid radicals. ROS induce lipid peroxidation and can damage DNA and proteins. Antioxidant enzymes, such as superoxide dismutase and peroxidase, help protect cells from oxidative stress, but if this system does not work properly and ROS cannot be removed, various conditions may develop, including high blood pressure, cancer, and diabetes (Lee, 2021). Several methods, such as oxygen radical absorbance capacity, hydroxyl radical antioxidant capacity, total peroxyl radical trapping antioxidant parameter, cupric ion reducing antioxidant capacity, ferric reducing antioxidant power, 2,2-diphenyl-1-picryl-hydrazyl-hydrate (DPPH), and 2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS), are used to measure antioxidant activity as determined by their ability to scavenge ROS (Munteanu & Apetrei, 2021).

The inflammatory response is an immune response that restores damaged tissues from external stimuli such as stress and injury. Inflammation is regulated by inflammatory mediators and cytokines secreted from macrophages, and synthesis of inflammatory factors such as nitric oxide (NO) and prostaglandin E_2 (PGE_2) may be induced by lipopolysaccharide (LPS) and reactive nitrogen species (Cho et al., 2009). When the production of inflammatory mediators increases, diseases such as diabetes, cancer, and atherosclerosis can develop; thus, it is important to suppress the generation of these inflammatory mediators (Liu et al., 2016; Yu et al., 2016).

Bacterial infection and the development of resistant bacteria continue to be serious concerns worldwide, necessitating the development of new antibacterial agents (Moghadamtousi et al., 2014). *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cereus*, and *Salmonella typhimurium* are well known food-borne pathogens (Al-Zoreky, 2009; Kanatt et al., 2010). Research to identify marine algal extracts that are active against these bacteria is being actively conducted (Shannon & Abu-Ghannam, 2016). To date, research on *Symphyocladia* has been limited to *S. latiuscula*. Therefore, we examined another species, *S. linearis*, to determine its biological activity and potential use as an antioxidative, anti-inflammatory, or antibacterial agent.

Materials and Methods

Algal material and extraction

S. linearis specimens were collected in April 2018 from Gangneung-si city, Gangwon-do province, Korea, and deposited at the National Marine Biodiversity Institute of Korea (MABIK).

Freeze-dried whole seaweed of *S. linearis* (30 g) was extracted by sonication using 70% ethanol (EtOH; 300 mL × 3) for 1 h, and evaporated to dryness by heating under reflux in vacuo. The dried 70% EtOH *S. linearis* extract (3.16 g dry weight) was stored at –80℃ until biological activity assessment.

Cell culture and cell viability assay

RAW 264.7 macrophages (ATCC, USA) were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 μg/mL) in a humidified incubator with 5% CO_2 at 37℃.

To assess cell viability, 100 μL of RAW 264.7 macrophages was seeded in triplicate at a density of 3×10^5 cells/mL in wells of a 96-well plate and cultured for 20–24 h. After removing the DMEM, 10 μL of *S. linearis* extract in 80 μL of fresh medium was added to each well and the samples were incubated for 30 min. Subsequently, 10 μL of LPS was added and the samples were incubated for 20–24 h. Finally, 10 μL of Cell Counting Kit-8 reagent (Dojindo Laboratories, Japan) was added and the samples were allowed to react for 2 h. Thereafter, the sample absorbance in each well was measured at 450 nm using a microplate reader.

Measurement of antioxidant activity

A slightly modified version of a method described by Blois

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(1958) was used to measure the DPPH radical scavenging activity of the *S. linearis* extract. Specifically, 100 μL of various concentrations (10–100 μg dry weight extract/mL) of the *S. linearis* extract was added to 100 μL of a 150 μM DPPH solution in a 96-well plate. The plate was shaken vigorously and placed in the dark at room temperature for 30 min, after which the absorbance of each sample was measured at 516 nm. The DPPH radical scavenging activity of the *S. linearis* extract was calculated and expressed as the half maximal inhibitory concentration (IC_{50}) value.

The ABTS radical scavenging activity of the *S. linearis* extract was measured using a slightly modified version of a method described by Re et al. (1999). $ABTS^{\bullet+}$ was produced by mixing a 7 mM aqueous stock solution of $ABTS^{\bullet+}$ with 2.45 mM potassium peroxodisulfate in the dark at 4℃ for 16 h. The stock solution was diluted with EtOH to an absorbance of 0.700 ± 0.100 at a wavelength of 734 nm. Various concentrations (10–100 μg dry weight extract/mL) of the *S. linearis* extract (100 μL) were added to wells containing 100 μg/mL of $ABTS^{\bullet+}$ solution in a 96-well plate. The plate was shaken vigorously and placed in the dark at room temperature for 15 min. The absorbance was then measured at 734 nm against a blank test.

The inhibition of ROS generation by the *S. linearis* extract was measured using a method described by Lee et al. (2021). RAW 264.7 cells were cultured in 96-well plates (3×10^5 cells/mL) and incubated at 37℃ for 24 h. The cells were then incubated with 5 μM 2',7'-dichlorofluorescin diacetate (DCFH-DA) for 30 min in the dark, treated with various concentrations (10–100 μg dry weight extract/mL) of the *S. linearis* extract, and incubated again for 30 min. The cells were then exposed to 10 μg/mL LPS for 24 h. ROS production was measured by recording the fluorescence at an excitation/emission wavelength of 492/525 nm using a fluorescence microplate reader.

Measurement of anti-inflammatory activity

Inhibition of NO production by the *S. linearis* extract was measured using a method described by Lee et al. (2021). RAW 264.7 cells were plated in 12-well plates (3×10^5 cells/mL) and upon confluency they were treated with various concentrations (10–100 μg/mL) of the *S. linearis* extract and 100 μg/mL LPS for 24 h. Thereafter, the NO produced was measured using the Griess reagent kit (Invitrogen, USA). The absorbance of each sample well was measured at 548 nm using a microplate reader and inhibition of NO production by the *S. linearis* extract was expressed as a percentage (%) of the LPS-stimulated group value.

Inhibition of PGE_2 production by the *S. linearis* extract was measured using a method described by Lee et al. (2021). RAW 264.7 cells were plated in 12-well plates (3×10^5 cells/mL) and upon confluency they were treated with various concentrations of the *S. linearis* extract (10–100 μg/mL) and 100 μg/mL LPS for 24 h. Thereafter, PGE_2 production was measured using a PGE_2 high sensitivity enzyme immunosorbent assay kit (Enzo, Japan). The absorbance of each sample well was measured at 405 nm using a microplate reader and inhibition of PGE_2 production by the *S. linearis* extract was expressed as a percentage (%) of the LPS-stimulated group value.

Measurement of antibacterial activity

The antibacterial activity of the *S. linearis* extract was tested against four reference microbial strains (*S. aureus* ATCC 6538P, *B. cereus* ATCC 14579, *E. coli* KCTC 2571, and *S. typhimurium* KCTC 1925) using the disc diffusion method and calculating the minimum inhibitory concentration (MIC) of the extract. A bacterial suspension (1×10^8 CFU/mL) was spread on Müeller Hinton Agar plates. An aliquot of *S. linearis* extract was then placed on the paper discs in the inoculated plates. The plates were allowed to stand for 15 min at room temperature, after which they were incubated at 35 ± 2℃ for 16–18 h. The diameters of the inhibition zones were measured in millimeters and all tests were performed in triplicate. To evaluate the MIC of the *S. linearis* extract, the extract was diluted in each liquid medium, the concentration of the test bacteria was measured by suspending it at a concentration of 2–8 × 10^5 CFU/mL, and the test bacteria was serially diluted two-fold in Müeller Hinton broth. Thus, the concentration range was determined. After incubation at 35 ± 2℃ for 16–20 h, the minimum concentration of algal extract at which no bacterial growth was observed was determined to be the MIC.

Statistical analysis

All data in this study are presented as means ± SD of triplicate experiments and analyzed using SPSS (PASW statistics 18). A $p < 0.05$ was considered statistically significant.

Results

Antioxidant activity

The potential cytotoxicity of the *S. linearis* extract was measured in cell experiments, revealing that a concentration range of 10–100 μg dry weight extract/mL did not reduce the viability of

LPS-stimulated RAW 264.7 cells (Fig. 1A). Therefore, a concentration range of 10–100 μg/mL extract was chosen for subsequent experiments. The IC_{50} values for DPPH and ABTS of the *S. linearis* extract were 34.57 and 11.70 μg/mL, respectively (Table 1). The inhibition of ROS production by the *S. linearis* extract was 12.8%, 38.2%, 49.3%, and 48.8% at 10, 25, 50, and 100 μg/mL, respectively (Fig. 1B). The *S. linearis* extract demonstrated greater antioxidant activity than the LPS-treated (control) group at all concentrations of extract.

Anti-inflammatory activity

The anti-inflammatory activity of the *S. linearis* extract was evaluated based on inhibition of NO and PGE_2 production in LPS-stimulated RAW 264.7 cells. *S. linearis* extract inhibited NO production by 10.0%, 42.1%, 61.1%, and 78.0% at 10, 25, 50, and 100 μg/mL extract, respectively (Fig. 2A). In turn, PGE_2 production was inhibited 1.5%, 69.1%, 83.2%, and 94.8% at 10, 25, 50, and 100 μg/mL extract, respectively (Fig. 2B). The inhibitory effect of *S. linearis* extract at 100 μg/mL on PGE_2 production (94.8%), in particular, is indicative of the strong anti-inflammatory effect of the extract.

Antibacterial activity

The *S. linearis* extract inhibition zones obtained using the disc diffusion method were 10 mm and 8 mm against *S. aureus* and *B. cereus*, and the MIC was 256 μg/mL and 1,024 μg/mL extract, respectively (Table 2). Our experimental results showed that the *S. linearis* extract had a stronger effect on gram-positive bacteria

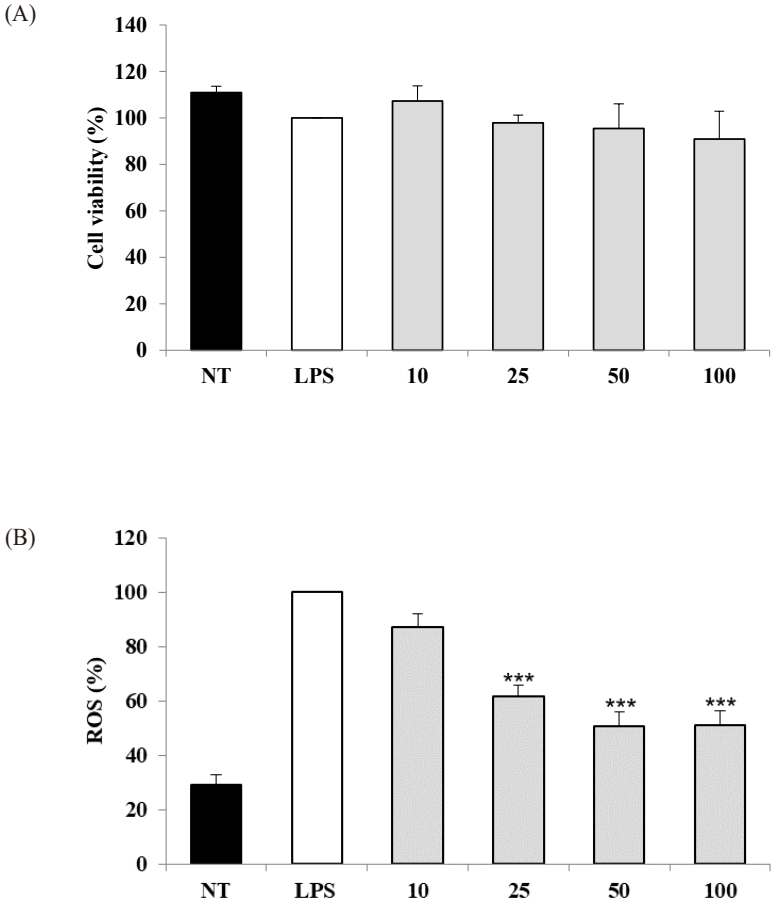

Fig. 1. Effect of *Symphyocladia linearis* extract (10–100 μg/mL) on cell viability (A) and production of ROS (B). RAW 264.7 cells were pretreated with different concentrations of *S. linearis* extract (10–100 μg/mL) and then exposed to LPS. All data are expressed as a percentage (%) of the NT. The experiment was performed in triplicate and data are presented as mean ± SD. $^{***}p$ <0.001 versus the LPS-stimulated group. NT, untreated control; LPS, lipopolysaccharide; ROS, reactive oxygen species.

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Table 1. DPPH and ABTS radical scavenging activity of *Symphyocladia linearis* extract expressed as the IC_{50}

Sample	DPPH (IC_{50})	ABTS (IC_{50})
S. linearis extract (μg/mL)	34.57 ± 0.36[1)]	11.70 ± 0.05

[1)] Data are expressed as the mean ± SD (n = 3).
IC_{50}, half-maximal inhibitory concentration.

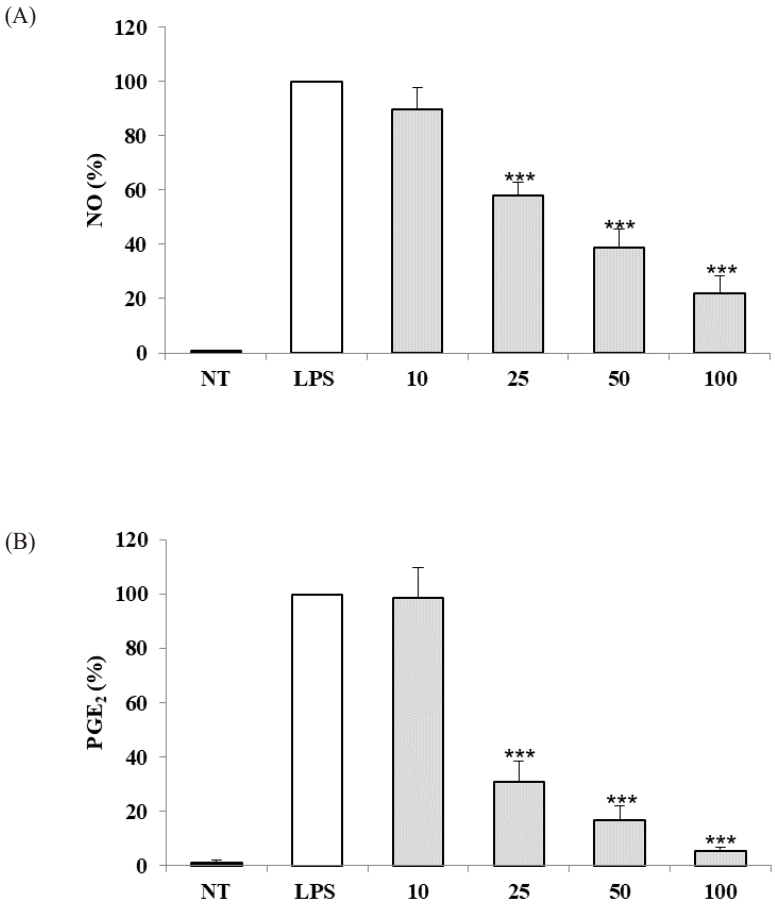

Fig. 2. Effect of *Symphyocladia linearis* extract (10–100 μg/mL) on NO (A) and PGE_2 (B) production. RAW 264.7 cells were pretreated with different concentrations of *S. linearis* extract (10–100 μg/mL) and then exposed to LPS. All data are expressed as a percentage (%) of the NT. The experiment was performed in triplicate and data are represented as mean ± SD. $^{***}p$ <0.001 versus the LPS-stimulated group. NT, untreated control; LPS, lipopolysaccharide; NO, nitric oxide; PGE_2, prostaglandin E_2.

Table 2. Paper disc diffusion assay and MIC of *Symphyocladia linearis* extract against four bacterial strains

Assay	*Escherichia coli* KCTC 2571	*Salmonella typhimurium* KCTC 1925	*Staphylococcus aureus* ATCC 6538P	*Bacillus cereus* ATCC 14579
Paper disc diffusion (mm)	-	-	10	8
MIC (μg/mL extract)	-	-	256	1,024

MIC, minimum inhibory concentration.

than on gram-negative bacteria.

Discussion

The existing literature on red algae includes reports on the biological activity (anti-diabetic, antioxidant, and antiviral) and chemical composition of *S. latiuscula*, which is registered and used as a food ingredient in Korea. The lesser-known species *S. linearis* was reported as a new species in 2013 by Kang & Kim (2013); however, to our knowledge, there have been no studies on its biological activity. Therefore, in this study we investigated the antioxidant, anti-inflammatory, and antibacterial activity of a 70% EtOH extract of *S. linearis*.

S. linearis extract exhibited weaker antioxidant activity (considering both DPPH and ABTS) than that previously reported the IC_{50} value for DPPH of *S. latiuscula* MeOH extract was 9.03 μg/mL and the ABTS radical scavenging effect of *S. latiuscula* EtOH extract was 3.8% at 60 μg/mL (Cho et al., 2012; Park et al., 1998). Additionally, inhibition of ROS production by the *S. linearis* extract (even when assayed at a high concentration of 100 μg/mL) was ≤ 50% (Fig. 1B), whereas inhibition by the *S. latiuscula* extract was 50.6% at 25 μg/mL (Kang et al., 2004). These results suggest that an equivalent extract of *S. linearis* has lower antioxidant activity than that of *S. latiuscula* extract.

In the assessment of the anti-inflammatory activity of *S. linearis* extract, increasing inhibition of NO and PGE_2 production occurred in a concentration-dependent manner. The *S. linearis* extract inhibited NO production > 50% at a concentration of 50 μg/mL and that of PGE_2 at a concentration of 25 μg/mL extract, showing that the extract exhibited high anti-inflammatory activity. PGE_2 not only serves as a mediator of the inflammatory response, but it also promotes Th2-type immune responses, suppresses Th1-type immune responses, and suppresses the production of inflammatory cytokines such as tumor necrosis factor-α, interleukin (IL)-1β, and IL-8 and anti-inflammatory cytokines such as IL-10. PGE_2 is known as an immune response modulator that promotes the production of cytokine (Harris et al., 2002). Our study, therefore, suggests that *S. linearis* could potentially be used in the prevention and treatment of inflammatory and immune diseases.

In the evaluation of the antibacterial activity of the *S. linearis* extract, we found that it was effective only against gram-positive bacteria (e.g., *S. aureus* and *B. cereus*), and was particularly effective against *S. aureus* (MIC of 256 μg/mL). *S. aureus* is one of the most common gram-positive bacteria that causes food poisoning in people (Rauha et al., 2000). In a previous study, a MeOH extract of *S. latiuscula* showed a MIC of 500 μg/mL extract for *S. aureus* and *E. coli* (Lim et al., 2000). It is difficult to compare the results because the extract types differed, MeOH vs. EtOH; however, it appears that *S. linearis* and *S. latiuscula* extracts exhibit similar antibacterial activity.

Based on our findings, we propose that a 70% EtOH extract of *S. linearis* has greater potential as an anti-inflammatory material than as an antioxidant or antibacterial material.

Conclusion

To the best of our knowledge, there have been no research studies on the biological activity of *S. linearis*; thus, we conducted experiments to assess the antioxidant, anti-inflammatory, and antibacterial properties of a 70% EtOH extract of *S. linearis*. Our results showed that *S. linearis* extract possesses strong anti-inflammatory properties, and therefore has the potential to be used in the prevention and treatment of inflammatory and immune diseases.

Competing interests

No potential conflict of interest relevant to this article was reported.

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Not applicable.

Availability of data and materials

Upon reasonable request, the datasets of this study can be available from the corresponding author.

Ethics approval and consent to participate

This article does not require IRB/IACUC approval because there are no human and animal participants.

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