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An Ethanol Extract of the Brown Seaweed *Hizikia fusiformis* and Its Active Constituent, Fucosterol, Extend the Lifespan of the Nematode *Caenorhabditis elegans*

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The short-lived nematode *Caenorhabditis elegans* has been used as a model organism for many studies, including lifespan extension. To screen common seaweeds for natural anti-aging agents, the lifespan of *C. elegans* (N2 wild-type strain) was measured by its hatch rate, growth rate, survival rate, chemotaxis, brood size, and egg-laying time after exposure to nematode growth medium (NGM) containing seaweed extracts. Approximately 30 animals synchronized at the first larval stage were incubated until they reached their adult stages before laying their eggs and were transferred to fresh NGM every 3 days. We also identified the major active compound from the seaweed by gas chromatography–mass spectrometry and tested its optimal dose for longevity. Of 13 common seaweed species, an ethanol extract of the brown seaweed *Hizikia fusiformis* showed the greatest effect on hatching, growth, and survival rates. The lifespan of *C. elegans* was significantly expanded 1.54-fold and 1.23-fold in the presence of the ethanol extract (0.05 mg/ml) and the main active component, fucosterol (0.05 mg/ml), respectively. Exposure to the ethanol extract also increased chemotaxis 1.13-fold, decreased brood size 0.74-fold, and shortened egg-laying time 0.96-fold. These results suggest that the aquaculturable *H. fusiformis* may be a promising source of a diet supplement to support health care.

Key words : *Caenorhabditis elegans*, fucosterol, *Hizikia fusiformis*, lifespan

Introduction

Various seaweed species are used as health foods and in traditional medicine in East Asia [4, 23]. As a source of bioactive substances, they have anticancer [20], antiobesity [15], antioxidative and anti-aging [17] effects, and so on. The brown seaweed *Hizikia fusiformis* (Harvey) Okamura, commonly known as *tot* in Korean, is an aquaculturable perennial seaweed that grows up to 1 m long. This name is currently regarded as a synonym of *Sargassum fusiforme* Harvey [7]. The amount of *H. fusiformis* produced by aquaculture in 2016 was 32,762 t (wet weight), and an additional 1,514 t (wet weight) was collected from natural populations [12]. This seaweed is abundant along temperate coastal regions of the northwestern Pacific Rim, including Korea, Japan, and China. The seaweed is promising as an ingredient in salad and as an additive to rice cooking because of its dietary fiber, bulky biomass, and potential for health benefits [3]. Furthermore, seaweeds containing antioxidants such as carotenoids and phenolics are known to contribute to the anti-aging process in humans [24].

Nematodes, especially *Caenorhabditis elegans*, are commonly used as model animals for studies of the aging process [18], gene expression [10], and the neuron system [21]. *C. elegans* posesses most human disease genes and disease pathways [22]. It is free-living, approximately 1 mm in length, and transparent and can be cultured either on agar or in broth medium with *Escherichia coli* as feed [19]. *C. elegans* has a short life cycle and lifespan. Most self-fertilized hermaphrodites can produce about 300 eggs. Having a short lifespan and easy propagation makes this roundworm ideal

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for lifespan assays.

No study has examined compounds from seaweeds as potential agents accountable for the longevity effect so far. Therefore, this study aimed to screen common seaweeds for natural anti-aging agents to extend the lifespan of *C.elegans*. With the ethanol extract of *H. fusiformis* (HFE) as the most promising seaweed, the hatch rate, growth rate, survival rate, chemotaxis, brood size, and egg-laying time were evaluated. Additionally, we identified the main active constituent from HFE as fucosterol and tested its optimal concentration for longevity.

Materials and Methods

Extract preparation and reagents

Thilli of 12 common seaweeds from Korea and one (*Kappaphycus alvarezii*) from Indonesia were collected and washed thoroughly to remove epiphytes. They were dried under shade at room temperature (RT) for 1 week, pulverized, and kept at -20℃ until further uses. For the ethanol extract, the powder was mixed with 95% ethanol at a ratio of 1:50(w/v) on a shaker at 200 rpm at RT for 1 day in the dark. The extract was dried under a stream of nitrogen gas and dissolved in 5% Tween-80 to 20 mg/ml. For the water extract, the powder remaining after ethanol extraction was mixed with distilled water (1:50, w/v), boiled for 10 min, centrifuged at 3,000× *g*, dried the supernatant at 65℃, and dissolved in distilled water to 20 mg/ml. Both the extracts were stored in airtight vials at -20℃ for further experiments. All reagents used were of analytical grade and purchased from Sigma-Aldrich Co. (St. Louis, MO, USA), unless otherwise stated.

C. elegans culture

The nematode *C. elegans* Bristol strain N2 (wild-type) obtained from the Caenorhabditis Genetics Center at the University of Minnesota was cultured in nematode growth medium (NGM) agar (3 g NaCl, 2.5 g peptone, 5 mg cholesterol, 1 mM $CaCl_2$, 1 mM $MgSO_4$, 17 g agar, 25 mM KPO_4 buffer, pH 6, 1 l H_2O) [19]. First, 3 ml of NGM agar or broth was poured into 3.5-cm plates and left for 2 day to detect contamination, after which 100 µl of *E. coli* OP50 was added as feed. The nematode was cultured at 20℃ on NGM agar, unless otherwise stated. The *E. coli* was grown in LB broth (10 g tryptone, 5 g yeast extract, 5 g NaCl, 1 l H_2O, pH 7) overnight and killed at 65℃ for 30 min before seeding onto NGM plates for the assays. Synchronization for age matching of *C. elegans* was conducted in a bleach solution [1.45 ml of 5.67% NaClO (Clorax, Yuhan Yangheng, Seoul, Korea), 0.25 ml of 10 M NaOH, 3.3 ml H_2O]. After 5 min, the lysis and survival rates were 100% and 85±4%, respectively. Approximately 30 adult animals were exposed to 500 µl of bleach solution for 5 min, and the eggs released were washed with M9 buffer (22 mM KH_2PO_4, 42 mM Na_2HPO_4, 86 mM NaCl, 1 mM $MgSO_4$) three times by centrifugation at 400× *g* for 2 min.

Hatch, growth, and survival rates

To compare the effects of different seaweed species, egg hatching was tested using more than 100 eggs in 3 ml of NGM broth containing seaweed ethanol or water extract (0.05 mg/ml) at 20℃. Eggs were observed under a microscope (Mitic AE 2000, Kowloon, Hong Kong) at 40× magnification. The hatch rate (%) is expressed as numbers of hatched eggs after 1 day against total eggs tested. The growth rate (%) of animals (n≥30) cultured in 3 ml NGM containing each seaweed extract (0.05 mg/ml) at 20℃ was expressed as [(body length at day 2 - body length at day 1) / body length at day 1] ×100. The length was measured using Image J software (ver. 1.45) under a microscope. The survival rate (%) was expressed as the number of living animals at day 30 at 20℃ against the number of animals tested in unchanged NMG broth containing each seaweed extract and live *E. coli*.

Life span

Lifespan was measured on both NGM agar and broth containing HFE (up to 1 mg/ml in 5% Tween-80), fucosterol (up to 0.1 mg/ml in 2% DMSO), or the control (5% Tween-80 or 2% DMSO). Approximately 30 synchronized animals at the first larval stage (L1) were incubated until adult stage L4 (before laying their eggs), transferred to NGM containing 5-fluorodeoxyuridine (FUDR; 25 mM) for 24 hr, and then transferred to fresh NGM without FUDR every 3 days. Killed *E. coli* was fed to each culture. Their lifespan was measured by calculating the number of living animals until all died.

Chemotaxis, brood size, and egg-laying time

For the chemotaxis assay, synchronized 3- and 7-day-old-animals (n=120) grown on NGM agar containing HFE (0.2 mg/ml) were placed in the middle area of a 10-cm standard

agar plate (20 g agar, 1 mM $CaCl_2$, 1 mM $MgSO_4$, 5 mM KPO_4, pH 6, 1 l H_2O) [5]. After adding 2.5 μl NaN_3 (0.25 M) to immobilize animals within the target area, the number of animals in the area containing the attractant (10 μl of 1.25 M NH_4Cl) or control were counted after 2 hr of incubation. Chemotaxis index = (A – C) / T, where A is the number of animals at the attractant, C is the number of animals at the control, and T is total animals used. The brood size of progeny numbers per each adult was measured on NGM agar containing HFE (0.2 mg/ml). Six synchronized L1 animals were transferred daily to fresh NGM containing extract and *E. coli* (killed) until no progenies were produced. Hatched progenies were counted 2 days later, when the animals reached the young adult stage. The total brood size was calculated by adding the numbers of progenies produced during the animals' lifetime. To examine effects of *H.fusiformis* extract on egg-laying time, approximately 30 animals at the L4 stage were placed on NGM agar, and egg-to-egg time was measured until the first egg was laid.

Analysis of chemical composition using GC-MS

Chemical composition of the HFE was analyzed by gas chromatography – mass spectrometry (GC-MS) using a QP 5050A instrument (Shimadzu, Kyoto, Japan) equipped with a flame-ionization detector and compared with spectral data from the database. Analysis was performed on an HP-5 column (30 m × 0.25 mm, 0.25 μm; Agilent Technologies, Santa Clara, CA, USA). The temperature was initially held at 50°C for 2 min and raised to 150°C at 4°C/min and to 250°C at 7°C/min. Helium carrier gas was controlled at 0.6 ml/min with a split ratio of 1:50. The mass spectrometer was operated in electron-ionization mode at 70 eV.

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Duncan's multiple range *post hoc* test and Student's *t*-test. Values are presented as means ± standard error (SE) of at least three independent experiments. Mean values denoted by different letters were significantly different ($p<0.05$).

Results

To compare the effects of 13 common seaweed species (12 Korean + 1 Indonesisan *K. alvarezii*) on lifespan extension in *C. elegans*, we prepared ethanol and water extracts from each seaweed and measured their anti-aging potential as indicated by hatching, growth, and survival rates (Table 1). When ethanol extracts were added to NGM broth to a final concentration of 0.05 mg/ml, *H. fusiformis*, *Saccharina japonica*, and *Ecklonia cava* showed significant positive effects on hatching rate (>90%) compared with the 5% Tween-80 con-

Table 1. Effects of seaweed extracts on hatching, growth, and survival rates in *C. elegans*

Species	EtOH extract (0.2 mg/ml)			Water extract (0.2 mg/ml)		
	Hatch rate (%)	Growth rate (%)	Survival rate (%)	Hatch rate (%)	Growth rate (%)	Survival rate (%)
Codium fragile	54 ± 9	49 ± 4	14 ± 6	45 ± 5*	57 ± 3*	1 ± 1
Costaria costata	67 ± 4	50 ± 5	16 ± 7	45 ± 1*	50 ± 4*	5 ± 3
Ecklonia cava	93 ± 5*	51 ± 3*	41 ± 21	40 ± 1**	45 ± 2*	17 ± 4*
Enteromorpha pertusa	83 ± 3	58 ± 3*	18 ± 10	49 ± 3*	53 ± 4*	8 ± 4
Gelidium amansi	80 ± 9	73 ± 4**	11 ± 2	79 ± 12	42 ± 2	8 ± 4
Gracilaria verrucosa	88 ± 7	61 ± 8*	14 ± 3	76 ± 9	56 ± 8*	7 ± 2
Gracilariopsis chorda	87 ± 7	54 ± 7	43 ± 8	63 ± 25	41 ± 4	3 ± 3
Hizkia fusiformis	95 ± 3**	37 ± 10	64 ± 6*	51 ± 2*	11 ± 2	11 ± 10
Kappaphycus alvarezii	66 ± 4	51 ± 4*	32 ± 7	53 ± 7	53 ± 3*	18 ± 4*
Porphyra yezoensis	68 ± 7	53 ± 7	23 ± 4	61 ± 2	64 ± 4**	5 ± 3
Saccharina japonica	94 ± 4*	44 ± 7	14 ± 7	49 ± 6*	49 ± 4*	9 ± 5
Sargassum fulvelum	84 ± 3	53 ± 6*	18 ± 4	74 ± 13	56 ± 3*	8 ± 2
Undaria pinnatifida	87 ± 8	44 ± 4	50 ± 2	46 ± 3*	51 ± 5*	2 ± 2
Control	79 ± 6	26 ± 8	30 ± 8	80 ± 8	20 ± 9	2 ± 1

Eggs (n≥100) or animals (n≥30) were cultured in 3 ml of NGM broth containing an ethanol or water extract of each seaweed (0.2 mg/ml) at 20℃. Hatch rate (%) is expressed as the number of hatched eggs at day 1 against the total eggs tested. Growth rate (%) is expressed as [(body length at day 2 - length at day 1) / length at day 1] x100. Survival rate (%) is expressed as the number of living animals at day 30 against the number of animals tested. Means ± SE (n=3). *$p<0.05$ and **$p<0.01$.

trol (79%). Most water extracts repressed hatching; especially, *E. cava* water extract repressed the hatching rate down to 40%. Adding both ethanol and water extracts of *H. fusiformis* (0.05 mg/ml) into NGM produced the least body length growth, presumably indicating an inverse relationship with longevity. *Gelidium amansii* ethanol extract and *Porphyra yezoensis* water extract enhanced body length. Adding HFE significantly increased animal survival rate at d 30 to 64%, compared with the control (30%). Thus, we further investigated HFE for enhancement of *C. elegans* lifespan.

To evaluate the concentration dependency of the longevity effects, HFE up to 1 mg/ml (as a final concentration in NGM) was added to NGM agar and broth (Fig. 1A). The lifespan of animals grown on NGM agar increased at 0.05 mg/ml (p<0.05). The mean lifespan at 0.05 mg/ml was 30.4

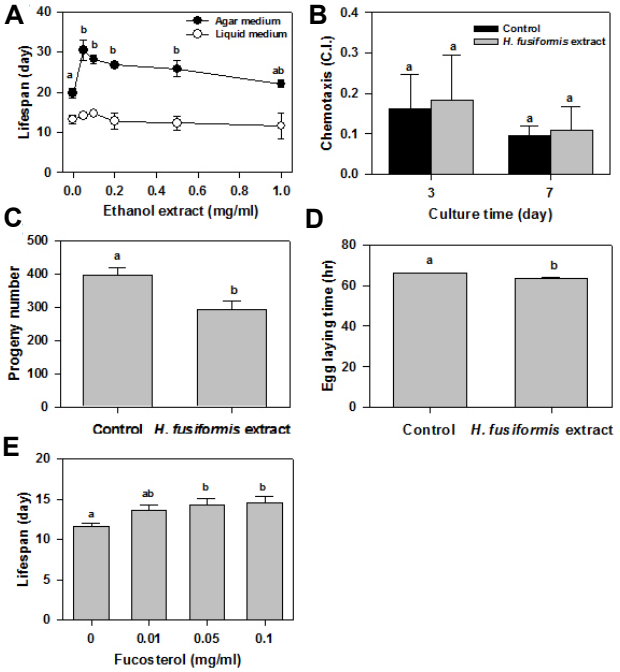

Fig. 1. Lifespan, chemotaxis, brood size, and egg-laying time in *C. elegans*. Lifespan of animals cultured on NGM agar and broth containing HFE was measured (A). Animals grown on NGM agar containing the extract (0.05 mg/ml) for 3 or 7 days were tested with the chemotaxis index (B). Brood size was calculated by number of progeny produced during the animals' lifetime (C). Egg-laying time was measured as the egg-to-egg time until the first egg was laid (D). Lifespan of animals cultured on NGM agar containing fucosterol was measured (E). Different letters (a-b) indicate significant differences compared with control (p<0.05). Data represent means ± SE.

days, a significant 154% increase compared to the control (19.7 days). At higher concentrations, the lifespan gradually decreased. Therefore, in subsequent experiments, HFE was added to animal cultures at 0.05 mg/ml as the final concentration. In NGM broth, the lifespan peaked at 0.1 mg/ml with a 111% increase compared to the control, and then decreased at higher doses.

Sensory function alterations could represent early indicators of life expectancy. By adding HFE (0.05 mg/ml), chemotaxis of the 3- and 7-day-old animals grown on NGM agar containing the extract increased slightly to 112% and 113%, respectively, compared to the control (Fig. 1B). This indicates that increasing trends in sensory functions with HFE appear to reflect lifespan extension, even though the values are not significantly different. Longevity has inverse correlations with fecundity and development; namely, long-lived animals have reduced brood size and delayed development time. With the addition of HFE (0.05 mg/ml), brood size of progeny per individual animal significantly decreased to 74% of the control (control: 396 progenies; extract group: 294) (p<0.05) (Fig. 1C). This indicates that reduced brood size with HFE demonstrates extension of lifespan. Developmental time or egg-laying time also sig-

Table 2. Profile of the major compounds in the ethanol extract of *H. fusiformis* using GC-MS

RT (min)	Compounds	Composition (%)
17.6	Myristic acid ($C_{14}H_{28}O_2$)	8.6
17.9	Loliolide ($C_{11}H_{16}O_3$)	0.9
18.0	Stearic acid ($C_{18}H_{36}O_2$)	0.4
18.6	Octadecyne ($C_{18}H_{34}$)	1.3
18.9	Pentadecanoic acid ($C_{15}H_{30}O_2$)	0.3
19.0	Neophytadiene ($C_{20}H_{38}$)	0.4
19.2	Tetramethyl-2-hexadecen-1-ol ($C_{20}H_{40}O$)	0.6
20.1	Hypogaic acid ($C_{16}H_{30}O_2$)	1.7
20.4	Palmitic acid ($C_{16}H_{32}O_2$)	57.3
20.9	Arachidic acid ($C_{20}H_{40}O_2$)	2.6
22.7	Eicosene ($C_{20}H_{40}$)	2.3
23.1	Oleic acid ($C_{18}H_{34}O_2$)	3.8
23.6	Gadoleic acid ($C_{20}H_{38}O_2$)	0.4
24.0	Nonacosanol ($C_{29}H_{60}O$)	0.4
25.6	Dipalmitic acid ($C_{35}H_{68}O_5$)	0.5
27.2	Hexadecanol ($C_{16}H_{34}O$)	0.2
29.0	Monopalmitin ($C_{19}H_{38}O_4$)	3.1
39.1	Euphadienol ($C_{30}H_{50}O$)	1.0
40.3	Fucosterol ($C_{29}H_{48}O$)	7.0
40.9	Campesterol ($C_{28}H_{48}O$)	1.5
–	Unknown compounds	5.7

Composition values are percentages of the relative peak areas.

nificantly decreased to 95% of the control (control: 66 hr; extract group: 63 hr) (p<0.05) (Fig. 1D). The delayed developmental time with HFE demonstrates extension of lifespan.

The chemical composition of the active HFE was analyzed by GC-MS. The major components by relative mass percentage were palmitic acid (57.3%), myristic acid (8.6%), and fucosterol (7.0%) (Table 2). Palmitic and myristic acids are common fatty acids in most organisms. Fucosterol is a phytosterol found in brown seaweed and has diverse biological activities to support nutraceutical applications. Therefore, we tentatively assumed that fucosterol was the main active constituent in HFE. Other minor sterol components such as campesterol and euphadienol and other compounds in HFE may also influence the effects of HFE on longevity. To evaluate the effects of the main active compound fucosterol on lifespan, fucosterol was added to NGM agar at final concentrations of up to 0.1 mg/ml (Fig. 1E). The lifespan of *C. elegans* significantly increased at 0.05 and 0.1 mg/ml fucosterol; therefore, we determined the optimal effective dose to be 0.05 mg/ml. The lifespan at this dose was 14.3 days, significantly increased to 123% compared to the control (11.6 days) (p<0.05).

Discussion

Using *C. elegans* as a model, the edible *H. fusiformis* was the most effective seaweed in extending lifespan. *H. fusiformis* has several health-promoting and beneficial nutrients, such as essential amino acids, n-3 polyunsaturated fatty acids (> 50% of total fatty acids), and dietary fiber (62% of biomass) [3]. It has also shown potent antioxiant [9], allelopathic [14], and proliferation activities on the osteosarcoma-derived cell line MG63 [8].

Deficits in sensory functions appear early in life, and sensory neuron functionality declines faster than locomotion during animal aging [16]. Wild-type 7-day-old *C. elegans* already showed strong impairment of their sensory functions. In these old animals, HFE showed a tendency to increase chemotaxis, albeit non-significantly. Preventing or retarding the loss of sensory functionality with HFE may accompany longevity of *C. elegans*. Moreover, we quantified the reduction in broodsize and the delay in egg-laying time, parameters that inversely correlated with lifespan [13]. HFE significantly reduced fecundity and delayed development; these changes might induce longevity by regulating over-activation of biological processes, such as development and reproduction leading to aging in adulthood [6].

One of the major phytosterols in HFE was fucosterol ($C_{29}H_{48}O$; CAS number 17605-67-3), which isolated from brown algae mostly. Fucosterol elevates the enzyme activities of free radical-scavenging superoxide dismutase, catalase, and glutathione peroxidase [11]. It also exhibits various biological activities, including antidiabetic, antioxidant, anti-photoaging, hepatoprotective, antihyperlipidemic, anti-inflammatory, anticancer, antimicrobial, anti-obesity, anti-atopic, anticholinergic, anti-osteoporotic, and angiotensin-converting enzyme inhibitory properties [1]. Sterols are important for mechanically strengthening membranes because they were competent in interactions with the phospholipid layers [2]. However, to date, no study has evaluated the effects of HFE and fucosterol on longevity. Although the underlying mechanisms for extending the lifespan of *C. elegans* or other animals are not clear, we assume that they may involve antioxidant-related effects during the aging process that increase longevity. Additionally, when HFE and fucosterol are compared, HFE shows generally higher longevity activities than fucosterol. This might be because of the presence of various active compounds in HFE and which provide synergistic effects. The practical synergic effects for lifespan from HFE compounds have not been determined yet, but our data suggest that the edible and aquaculturable *H. fusiformis* and/or fucosterol may have beneficial effects as a dietary supplement to support health care.

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초록 : 갈조류 톳(*Hizikia fusiformis*)의 에탄올추출물 및 이의 활성성분 fucosterol에 의한 예쁜꼬마선충의 수명 연장

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수명이 짧은 예쁜꼬마선충은 수명 연장 등 많은 연구의 모델생물으로서 사용되고있다. 해조류 추출물들이 포함된 선충배양용 한천배지에서 선충(N2 야생형)을 키우면서 그 수명을 측정하였다. 13종의 흔한 해조류 중에서 갈조류 톳의 에탄올추출물이 난 부화, 성장 및 생존율에서 가장 큰 효과를 보였다. 그 수명은 에탄올추출물(0.05 mg/ml) 및 주 활성성분인 fucosterol (0.05 mg/ml) 첨가에 의하여 1.54배 및 1.23배 정도로 유의미하게 증가되었다. 또한 에탄올추출물에 의하여 chemotaxis는 1.13배 증가, 한 배에서의 새끼는 0.74배 감소, 첫 산란시기는 0.96배 단축되었다. 이와 같은 결과들로 보아서 양식 가능한 해조류 톳은 건강에 이로운 건강보조 식품으로서의 좋은 재료가 될 수 있을 것이다.