Scientific Research Publishing

Food and Nutrition Sciences, 2025, 16(5), 729-740
https://www.scirp.org/journal/fns
ISSN Online: 2157-9458
ISSN Print: 2157-944X

Plasmalogen-Containing Scallop-Derived Lipids Affect the Endocrine System of *Caenorhabditis elegans* Nematodes and Improved Its Lifespan and Health

Riku Inoue, Kazuichi Sakamoto*

Faculty of Life and Environmental Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan
Email: 08274236riku1@gmail.com, *sakazbo@gmail.com

How to cite this paper: Inoue, R. and Sakamoto, K. (2025) Plasmalogen-Containing Scallop-Derived Lipids Affect the Endocrine System of *Caenorhabditis elegans* Nematodes and Improved Its Lifespan and Health. *Food and Nutrition Sciences*, **16**, 729-740.
https://doi.org/10.4236/fns.2025.166040

Received: March 24, 2025
Accepted: June 17, 2025
Published: June 20, 2025

Abstract

To analyze the effects of plasmalogen-containing scallop-derived lipids on lifespan, health span, and neuroendocrine status, we assessed the effects of these lipids on the lifespan, health (motility), aging (lipofuscin accumulation), oxidative stress resistance, and neurotransmitter (dopamine, serotonin, and oxytocin) levels of *Caenorhabditis elegans*. The administration of scallop-derived lipids extended the lifespan of *C. elegans* and suppressed the age-related reduction in movement. Additionally, its oxidative stress resistance increased, despite the higher intracellular levels of reactive oxygen species. Moreover, scallop-derived lipids reduced the accumulation of lipofuscin, which is an aging marker in nematodes, and increased the levels of neurotransmitters (dopamine, serotonin, and oxytocin). Furthermore, the gene expression levels of *pmk-1* (p38 mitogen-activated protein kinase 1) and *daf-16* (dauer formation-16) were increased. These results indicate that plasmalogen-containing scallop-derived lipids may extend the lifespan and health span of *C. elegans*, and affect its neurotransmitter secretion.

Keywords

Plasmalogen, *Caenorhabditis elegans*, Serotonin, Dopamine, Oxytocin, Lipofuscin

1. Introduction

Plasmalogens (Pls) are glycerophospholipids characterized by the presence of an aliphatic alcohol with a vinyl ether bond at the sn-1 position and polyunsaturated

fatty acids at the sn-2 position. In mammals, Pls account for up to 20% of total membrane lipids and are most common in the brain [1]. Pls are more susceptible to oxidation by reactive oxygen species (ROS) than other lipids owing to their vinyl ether bond, and are believed to protect cells from oxidative stress [2]. Pl levels decrease with age. Pl levels in the serum of the elderly are 40% lower than those in the young [3]. In a study by Han *et al.*, Pl levels were reduced in the brains of humans and mice [4]. This reduction in Pl levels has been confirmed in neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease [5] [6].

The hippocampus is crucial for memory. Hippocampal neuronal degradation through oxidative stress or amyloid beta accumulation results in reduced brain function, such as a decline in memory [7]. Pls enhance the phosphorylation of protein kinase B (Akt) and extracellular signal-regulated kinase (ERK) in neurons and prevent neuronal death by suppressing apoptosis [8]. Additionally, Pls suppress lipopolysaccharide (LPS)-induced brain inflammation and amyloid-β accumulation [9]. Moreover, the oral administration of Pls enhances behavior in Alzheimer's model rats and increases blood Pl levels [10].

Fujino *et al.* [11] administered 1 mg/day of scallop-derived Pls for 6 months to patients with mild Alzheimer-type dementia and healthy individuals with mild cognitive impairment (MCI). Therefore, the cognitive function assessment scale, Wechsler Memory Scale-Revised (WMS-R), was substantially enhanced in the treatment group, whereas no significant enhancement was observed in the placebo group, with a significant reduction in the plasma Pl levels [11].

Scallop-derived Pls were administered at 1 mg/day for 3 months to patients with major depressive disorder or persistent depressive disorder, in addition to the usual treatment. This administration demonstrated a marked enhancement in state and trait anxiety scores, physical and mental fatigue, mood and emotion scales, and sleep quality (feeling sleepy and refreshed upon waking up) [12].

Lewis and Fravel [13] administered scallop-derived lipids containing plasmalogens (SLPls) at a dose of 0.5 or 1 mg/day for 90 d to elderly individuals with cognitive impairment. Therefore, a significant enhancement occurred in the cognitive function assessment scale, mini-mental state examination (MMSE), and a clinically significant alteration was observed in the Center for Epidemiologic Studies Depression Scale (CES-D) depression rating scale, although no significant difference was observed [13].

The effect of SLPls on cognitive function enhancement and depression appears to be related to anti-inflammatory, neuroprotective, and antioxidant mechanisms, and amyloid-β accumulation suppression. However, the anti-aging effects of SLP1 and its effect on neurotransmitter secretion remain to be elucidated. The purpose of this study was to analyze the physiological effects of SLPI on aging (lifespan, aging-dependent motility, and lipofuscin accumulation) and secretion of neurotransmitters (dopamine, serotonin, and oxytocin) using the nematode *Caenorhabditis elegans* [14] [15] as a model organism, which is suitable for aging-related analysis.

2. Materials and Methods

2.1. Caenorhabditis Elegans

The *C. elegans* strain used in this study was N2 Bristol (wild type). Worms were cultured at 20˚C on nematode-growth medium (NGM) plates with *Escherichia coli* (OP50).

2.2. Synchronization Processing of *C. elegans*

To collect eggs, adult worms were crushed in a NaClO solution (containing 10 N NaOH [Wako Pure Chemical Industries, Ltd., Osaka, Japan] and NaClO [Haiter; Kao, Tokyo, Japan] mixed at a ratio of 1:10), and their growth levels were synchronized in this process.

2.3. SLPls

SLPls provided by Daiwa Pharmaceutical Co., Ltd. were extracted from the scallop mantle using ethanol, and the lipids obtained were powdered using γ-cyclodextrin to contain 0.34% ethanolamine Pls. The SLPls were dissolved in dimethyl sulfoxide (DMSO) (Kanto Chemical Co., Tokyo, Japan) to create a 100 mg/mL stock solution, which was stored at −20˚C. For the assays, SLPls and DMSO were individually mixed with *E. coli* OP50 to obtain final SLPl concentrations of 0.1, 1, and 5 mg/mL, and a final DMSO concentration of 5%. In preliminary experiments, we applied PLSI at concentrations ranging from 0.01 to 10 mg/mL, and determined that 0.1 and 5 mg/mL were appropriate for further experiments. This mixture was spread onto NGM plates at 200 μL/60 mm or 1000 μL/90 mm. For the control, DMSO was mixed with the *E. coli* OP50 solution to obtain a final concentration of 5% and spread on NGM plates.

2.4. Intracellular ROS Levels

Synchronized worms were cultured for 96 h on SLPl plates (0 control treatment [CT], 0.1, 1, and 5 mg/mL). Subsequently, worms were washed and collected in a 1.7-mL tube. Dichlorodihydrofluorescein diacetate (DCFH-DA) (Wako Pure Chemical Industries, Ltd.) was diluted with S-basal (0.01 mM cholesterol, 100 mM NaCl, and 50 mM potassium phosphate; pH 6.0) to produce a 50-μM DCFH-DA solution, and 400 μL was added to the tube containing worms. After shaking for 1 h and discarding the DCFH-DA solution, 10% ethanol was added to fix *C. elegans*. Fluorescence images were captured using a BZ8000 microscope (Keyence, Osaka, Japan) and analyzed using the ImageJ software. The fluorescence level of the control *C. elegans* was set at 100%, and 30 worms from each group were assessed. The experiment was repeated thrice.

2.5. Oxidative Stress Resistance

Synchronized worms were cultured for 96 h on SLPl plates (0 CT, 0.1, 1, and 5 mg/mL). Subsequently, they were transferred to each well of a 24-well plate con-

taining 400 μL of 0.05% hydrogen peroxide solution (H_2O_2; Sigma Aldrich Japan, Tokyo, Japan) (0^{th} hour). The survival rate was measured every hour from 2 h post-transfer. The survival rate at the 0^{th} hour was set at 100%, and 12 worms from each group were assessed. The experiment was repeated thrice.

2.6. Motility of *C. elegans*

Synchronized worms were cultured at 20˚C for 96 h on NGM plates containing *E. coli* OP50, transferred to SLPl plates (0 CT, 0.1, 1, and 5 mg/mL), and maintained at 20˚C. The transfer day was designated as day 0. Subsequently, worms were transferred to novel SLPl plates (0 CT, 0.1, 1, and 5 mg/mL) every 3 days. Thrashing movements were measured for 15 s on each transfer day. To prevent offspring generation, 0.5 mg/mL 2'-deoxy-5-fluorouridine (FUdR; [Wako Pure Chemical Industries, Ltd.]) was added to the plates on days −1, 0, and 3. Ten worms from each group were assessed. The experiment was repeated thrice.

2.7. Lipofuscin Accumulation

Synchronized worms were cultured at 20˚C for 96 h on NGM plates containing *E. coli* OP50, transferred to SLPl plates (0 CT, 5 mg/mL), and maintained at 20˚C. The day of transfer was designated as day 0. Subsequently, worms were transferred to novel plates containing SLPls (0 CT, 5 mg/mL) every 3 days. On day 18, worms were collected, photographed using a BZ8000 microscope (Keyence, Osaka, Japan), and analyzed using ImageJ software. To prevent offspring generation, 0.5 mg/mL FUdR (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was added to the plates on days −1, 0, and 3. The fluorescence level of the control worms was set at 100%, and the survival rate of 20 worms from each group was measured. The experiment was repeated thrice.

2.8. Lifespan Analysis

Synchronized worms were cultured at 20˚C for 96 h on NGM plates containing *E. coli* OP50, transferred to SLPl plates (0 CT, 5 mg/mL), and maintained at 20˚C. The day of transfer was designated as day 0. Subsequently, worms were transferred to novel plates containing SLPls (0 CT, 5 mg/mL) every 2 days. Live and dead worms were counted on each day of transfer, with dead worms defined as those unresponsive to gentle poking with a platinum picker. To prevent offspring generation, 0.5 mg/mL FUdR (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was added to the plates on days −1, 0, 2, and 4. The survival rate of 40 worms from each group was measured. The experiment was repeated thrice.

2.9. Neurotransmitter Levels

Approximately 3000 synchronized worms were cultured for 96 h on SLPl plates (0 CT, 5 mg/mL). Subsequently, cultured *C. elegans* were homogenized and centrifuged to recover the supernatant. Analyses were performed using a dopamine ELISA kit (ImmuSmol, Bordeaux, France), serotonin ELISA kit (ImmuSmol), and

oxytocin ELISA kit (Cayman Chemical Company, Ann Arbor, MI, USA) following the manufacturers' instructions. The experiment was duplicated four times and repeated thrice.

2.10. Gene Expression

Approximately 3000 synchronized worms were cultured for 96 h on SLPl plates (0 CT, 5 mg/mL) and homogenized. Following a reverse transcriptase reaction (PrimeScript RT Reagent Kit with gDNA Eraser, Takara, Shiga, Japan), real-time quantitative PCR (qPCR) was performed using a Thermal Cycler Dice Real Time System Lite (Takara Biotechnology Inc., Shiga, Japan) with Thunderbird SYBR Green Mix (Toyobo, Co., Osaka, Japan) and the primer sequences for each gene (dauer formation-16 [*daf-16*], age-related gene-1 [*age-1*], superoxide dismutase [*sod-1*], *sod-2*, *sod-3*, skinhead-1 [*skn-1*], neuronal symmetry-1 [*nsy-1*], p38 mitogen-activated protein kinase 1 [*pmk-1*], and *actin*). Actin was used as a reference gene. The experiment was duplicated three times and repeated thrice.

2.11. Statistical Analysis

Data were presented as the mean ± SEM, and statistical analysis was performed using one-way ANOVA followed by Tukey's HSD post hoc test. The survival rate was analyzed using the log-rank test. Graphs were generated using Microsoft Excel and Microsoft PowerPoint software (Microsoft Corp., Redmond, WA, USA). A P value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Lifespan

To assess the effect of SLPls on lifespan, the lifespan of the nematode worms was analyzed. The synchronized worms were transferred to SLPl plates (0 CT, 5 mg/mL) (day 0), and their survival rate was observed every two days. The plates were replaced every two days. The average lifespan was significantly extended in the SLPl-administered group compared with that in the control group (**Figure 1**). Additionally, the maximum lifespan was extended in the SLPl-administered group.

3.2. Motility

To assess the effect of SLPls on health, systemic movement (thrashing movement) of the worms was analyzed. The synchronized worms were transferred onto SLPl plates (0 CT, 0.1, 1, and 5 mg/mL) (day 0), and systemic whiplash movements were measured every 3 d for 15 s. The plates were replaced every 3 days. The movement frequency was significantly reduced as the culture progressed in the control group. In contrast, in the SLPl-administered group, the reduction in movement frequency, dependent on the number of culture days, was suppressed, and the movement frequency increased compared with that of the control group (**Figure 2**).

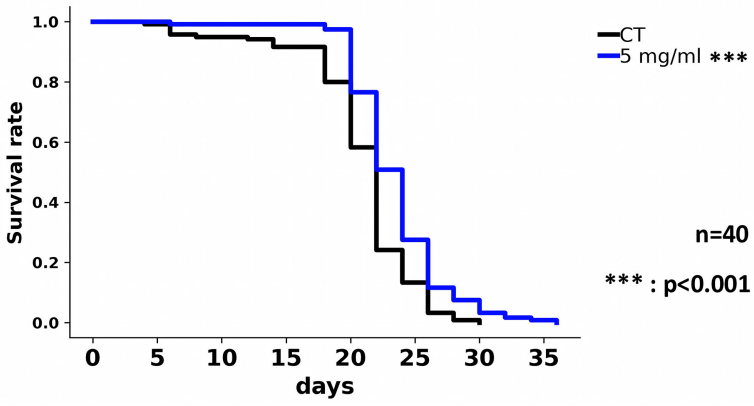

Figure 1. Lifespan analysis. Effect of SLPls on lifespan of wild type *C. elegans*. Worms were cultured at 20˚C on NGM-OP50 plates, treated with (5 mg/ml) or without (CT) SLPls. Survival of SLPl-treated and non-treated worms (n = 40 worms/group) was determined every two days. Statistical differences compared with the control (CT) were considered significant at ***P < 0.001 using the log-rank test. Data are represented by the mean ± SD. Experiments were performed in triplicate.

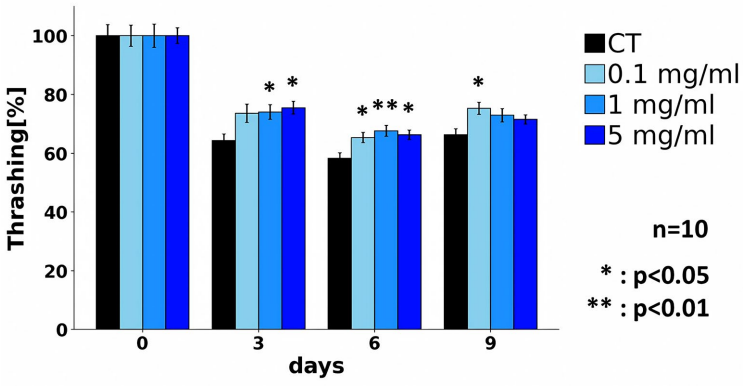

Figure 2. Motility analysis. Effect of SLPls on motility of wild-type *C. elegans*. Worms were cultured at 20˚C on NGM-OP50 plates, treated with (0.1, 1, 5 or mg/mL) or without (CT) SLPls for 96 h. Thrashing motility of SLPl-treated and non-treated worms (n = 10 worms/group) was measured every 3 days (0, 3, 6, and 9 days). Statistical differences compared with the control (CT) were considered significant at *P < 0.05 and **P < 0.01 according to the Tukey's HSD test. All assays were conducted three times independently.

3.3. Lipofuscin Accumulation

To assess the effect of SLPls on aging, the lipofuscin accumulation levels were measured. Synchronized worms were transferred onto SLPl plates (0 CT, 5 mg/mL) (day 0), and the plates were replaced every three days. When worms were collected on day 18 and observed under a fluorescence microscope (Keyence, BZ8000), the lipofuscin accumulation levels were significantly lower in the SLPl-administered group compared with those in the control group (Figure 3).

3.4. Intracellular ROS Levels

Synchronized worms were cultured on SLPl plates (0 CT, 0.1, 1, and 5 mg/mL) for 96 h, treated with DCFH-DA, and fluorescence was observed using a BZ8000 mi-

croscope (Keyence). Fluorescence was analyzed using the ImageJ software. The ROS levels increased based on the concentration of SLPls administered (Figure 4).

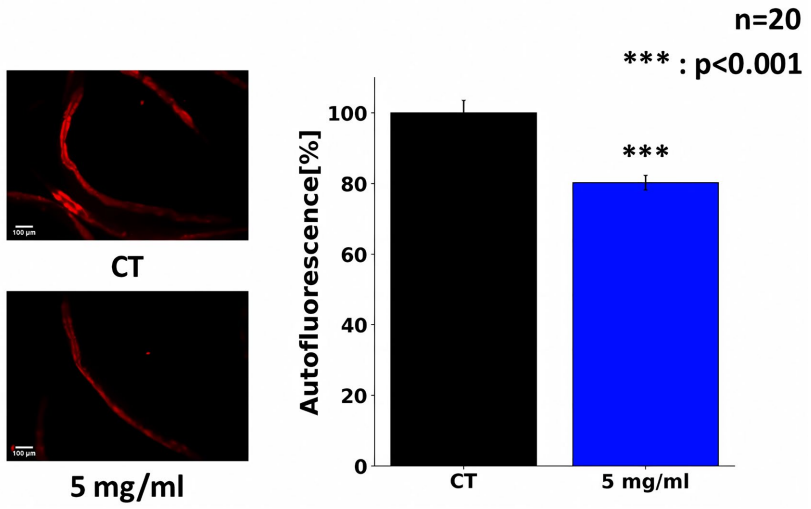

Figure 3. Lipofuscin accumulation. Effect of SLPls on lipofuscin accumulation in wild-type *C. elegans*. Worms were cultured at 20˚C on NGM-OP50 plates, and treated with (5 mg/mL) or without (CT) SLPls for 18 days. The lipofuscin accumulation level of worms (n = 20 worms/group) was observed under a fluorescence microscope (Keyence, BZ8000). Scale bars, 100 μm. Data are presented as the mean ± SEM. *P < 0.05, ***P < 0.001 according to the Tukey's HSD test. All assays were conducted three times independently.

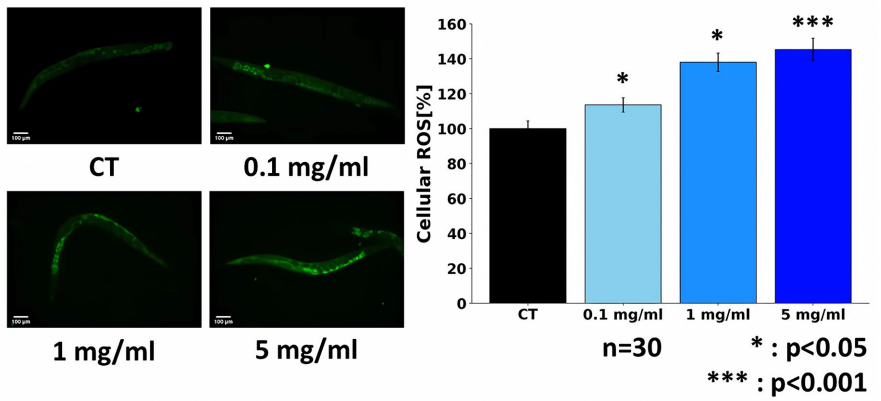

Figure 4. Intracellular ROS levels. Effect of SLPls on intracellular ROS levels of wild type *C. elegans*. Worms were cultured at 20˚C on NGM-OP50 plates, treated with (0.1, 1, or 5 mg/mL) or without (CT) SLPls for 96 h. Fluorescence images were captured using a BZ8000 microscope (Keyence, Osaka, Japan) and analyzed using ImageJ software. The fluorescence level of the control *C. elegans* was set at 100%, and 30 worms from each group were assessed. Scale bars, 100 μm. Data are presented as the mean ± SEM. *P < 0.05, ***P < 0.001 according to the Tukey's HSD test. All assays were conducted three times independently.

3.5. Oxidative Stress Resistance

Synchronized worms were cultured on SLPl plates (0 CT, 0.1, 1, and 5 mg/mL) for 96 h. The survival rate was measured every hour post-treatment with H_2O_2 solution. The survival rate of worms significantly increased depending on the concen-

tration of SLPls (Figure 5).

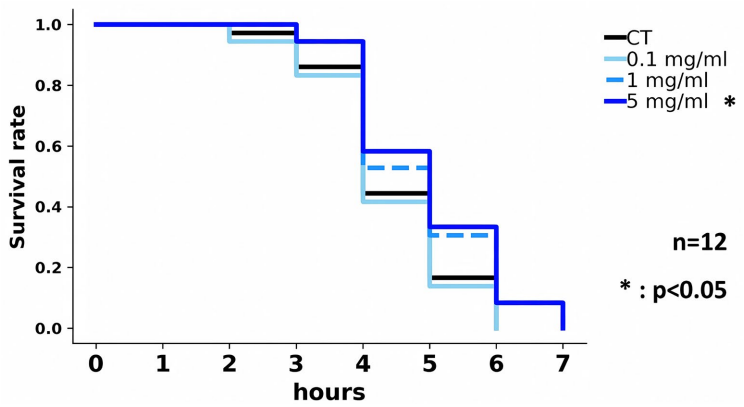

Figure 5. Oxidative stress tolerance. Effect of SLPls on stress tolerance of wild-type *C. elegans*. Worms were cultured at 20˚C on NGM-OP50 plates, treated with (0.1, 1, 5 mg/mL) or without (CT) SLPls for 96 h. Oxidative stress survival of worms exposed to 0.1% hydrogen peroxide (n = 12 worms/group). Statistical differences compared with control (CT) were considered significant at *P < 0.05 using the log-rank test. All assays were conducted thrice independently.

3.6. Endocrine Levels

To assess the effect of SLPls on the endocrine system, synchronized worms were cultured on SLPl plates (0 CT, 5 mg/mL) for 96 h. They were homogenized, and the dopamine, serotonin, and oxytocin levels were quantified using the ELISA method. The dopamine, serotonin, and oxytocin levels significantly increased in the SLPl-administered group compared with that in the control group (Figure 6).

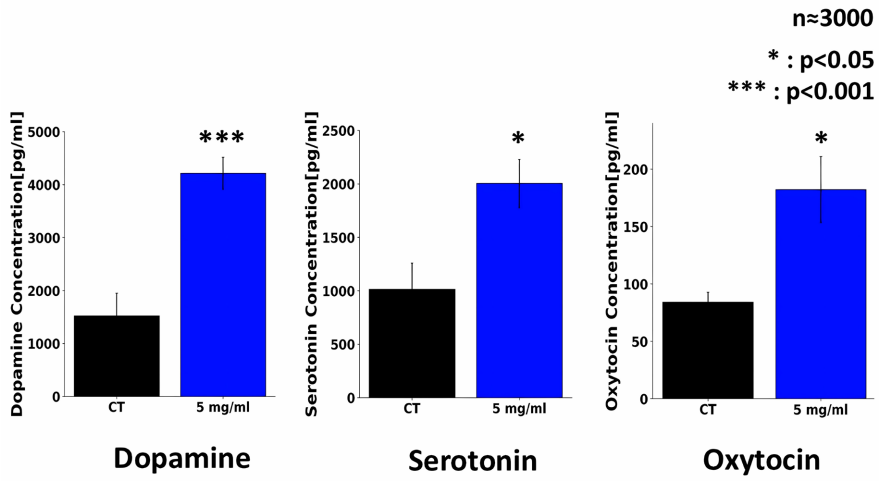

Figure 6. Endocrine levels. Effects of SLPls on the secretion levels of neurotransmitters (dopamine, oxytocin, serotonin) in wild-type *C. elegans*. Worms were cultured at 20˚C on NGM-OP50 plates, treated with (5 mg/mL) or without (CT) SLPls for 96 h (n ≈ 3000 worms/group). Neurotransmitter production was assessed, and its quantity in worm homogenate was determined by ELISA. Statistical differences compared with control (CT) were considered significant at *P < 0.05 and ***P < 0.001 using Student's *t*-test. The experiment was duplicated four times and repeated thrice.

3.7. Gene Expression

To assess the effect of SLPls on gene expression, the synchronized worms were cultured for 96 h on plates containing SLPls (0 CT, 5 mg/mL). The expression of genes associated with insulin/insulin-like growth factor (IGF)-like signal transduction and mitogen-activated protein kinase (MAPK) signaling pathways was analyzed using qPCR in worms treated with the homogenized extract. Although the activity of DAF-16 remains unclear, at least, *daf-16* gene expression level was increased approximately 1.6-fold by SLPIs. SLPIs also significantly increased gene expression of *age-1*, *skn-1*, *nsy-1* and *pmk-1* (Figure 7).

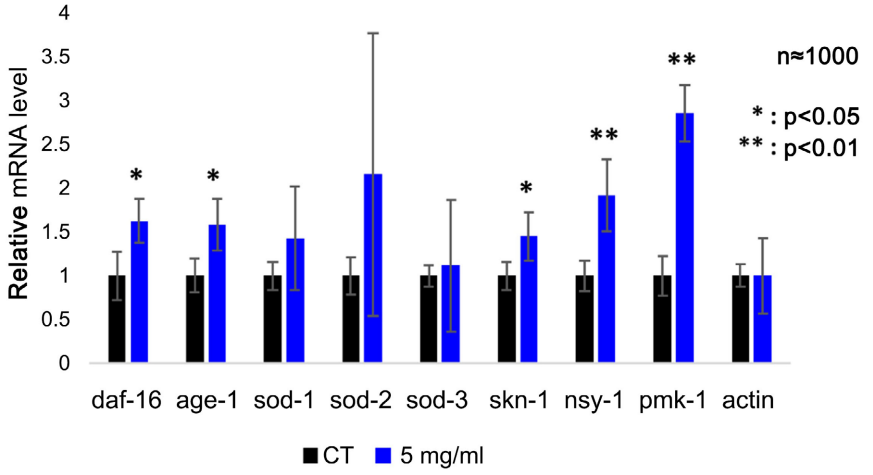

Figure 7. Gene expression. Effects of SLPls on the mRNA expression of genes (*daf-16*, *age-1*, *sod-1*, *sod-2*, *sod-3*, *skn-1*, *nsy-1*, *pmk-1*, and *actin*) in wild-type *C. elegans*. Worms were cultured at 20˚C on NGM-OP50 plates, treated with (5 mg/mL) or without (CT) SLPls for 96 h (n ≈ 3000 worms/group). Statistical differences compared with control (CT) were considered significant at *P < 0.05 and **P < 0.01 using multiple t-tests. Data are represented as the mean ± SD. The experiment was duplicated three times and repeated thrice.

4. Discussion

The administration of SLPls extended the lifespan and improved the health of *C. elegans* by suppressing age-associated motility reduction and lipofuscin accumulation while increasing oxidative stress resistance, despite the increased ROS levels. This may indicate that SLPls exhibit strong antioxidant activity. It is very interesting that oxidative stress resistance improved (Figure 5) despite the increase in intracellular ROS concentration (Figure 4). This may be due to the increased motility caused by the antioxidant effect of PLSI, which resulted in an increase in ROS. Alternatively, it is possible that the increase in intracellular ROS led to a kind of hormesis effect, which increased oxidative stress resistance.

Dopamine activates the MAPK signaling pathway, which is involved in lifespan regulation and stress responses [16]. Additionally, the dopamine receptor D2 (DOP-2) in *C. elegans* activates adenosine monophosphate (AMP) kinase, which further activates DAF-16, a transcription factor known as the longevity gene [17]. In this study, it was clarified that SLPls increase dopamine levels and have physiological

effects, such as the extension of lifespan. These findings indicate that SLPls increase the levels of dopamine, which activates AMP kinase and DAF-16 through the MAPK signaling pathway and DOP-2. Therefore, the physiological actions, such as extending lifespan, suppressing age-related reduction in motility, reducing lipofuscin accumulation, and increasing oxidative stress resistance, may have worked.

There are limited reports on the relationship between serotonin, oxytocin, and lifespan regulation, with numerous unclear aspects. However, certain studies indicate an interaction between serotonin and insulin/IGF-like signaling transduction pathways that regulate DAF-16, which antagonistically regulates lifespan [18]. In this study, it was clarified that SLPls increase serotonin and oxitocin levels, and that the mRNA expression of AGE-1, which suppresses DAF-16, increases. Therefore, the serotonin pathway may be involved in dopamine-mediated physiological actions. In *C. elegans*, decreased levels of dopamine, serotonin, and oxytocin and a decrease in motility occur with aging, whereas increased levels of dopamine and oxytocin are closely associated with the suppression of motility reduction [19] [20]. Therefore, it is possible that SLPls suppressed the reduction in age-related motility of *C. elegans* by increasing the levels of dopamine and serotonin. In this study, we have not used gene knockout mutants such as da-16 and age-1, etc. Therefore, future experiments using mutants are essential to clarify the molecular mechanisms involved in the physiological actions of SLP1s.

Pl administration has been reported to enhance cognitive function and exhibit antidepressant effects [11] [12]. Additionally, it is involved in neuronal death suppression by inhibiting apoptosis and reducing brain inflammation and amyloid-β accumulation [8] [9]. In contrast, as dopamine, serotonin, and oxytocin affect cognitive functions [21]-[23], an increase in their levels may also be involved in the effect of SLPls on cognitive function enhancement and depression [13].

This study confirmed that SLPls increased oxidative stress resistance and extended the lifespan of *C. elegans*. Additionally, SLPls suppressed aging and improved their health. Moreover, SLPls increased the levels of dopamine, serotonin, and oxytocin, potentially affecting neurotransmitter secretion. It is believed that Pls within SLPls may be responsible for these functions.

In the future, we will conduct experiments using mutants, such as a deletion mutant of DAF-16, which is a transcription factor that regulates aging and lifespan. Additionally, these experiments aimed to elucidate the mechanism of action underlying the effects of SLPls. Moreover, we will clarify the relationship between an increase in intracellular ROS levels, lifespan extension, and increased oxidative stress resistance, confirmed in this study using mutants.

Acknowledgements

Plasmalogen was kindly provided by Daiwa Pharmaceutical Co., Ltd. This work was partly supported by Grants-in-Aid for Scientific Research and Education from the University of Tsukuba, Japan, Venex Co., Ltd. (Kanagawa, Japan) and Daiwa Pharmaceutical Co., Ltd. (Tokyo, Japan). Role of the funding source: The

sponsors of the study had no role in the study design, data collection, analysis, result interpretation, article writing, or the decision of manuscript submission for publication.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Braverman, N.E. and Moser, A.B. (2012) Functions of Plasmalogen Lipids in Health and Disease. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular Basis of Disease*, **1822**, 1442-1452. https://doi.org/10.1016/j.bbadis.2012.05.008

[2] Farooqui, A.A. and Horrocks, L.A. (2001) Book Review: Plasmalogens: Workhorse Lipids of Membranes in Normal and Injured Neurons and Glia. *The Neuroscientist*, **7**, 232-245. https://doi.org/10.1177/107385840100700308

[3] Maeba, R., Maeda, T., Kinoshita, M., Takao, K., Takenaka, H., Kusano, J., *et al.* (2007) Plasmalogens in Human Serum Positively Correlate with High-Density Lipoprotein and Decrease with Aging. *Journal of Atherosclerosis and Thrombosis*, **14**, 12-18. https://doi.org/10.5551/jat.14.12

[4] Han, X., Holtzman, D.M. and McKeel, D.W. (2001) Plasmalogen Deficiency in Early Alzheimer's Disease Subjects and in Animal Models: Molecular Characterization Using Electrospray Ionization Mass Spectrometry. *Journal of Neurochemistry*, **77**, 1168-1180. https://doi.org/10.1046/j.1471-4159.2001.00332.x

[5] Mawatari, S., Fukata, M., Arita, T., Maruyama, T., Kono, S. and Fujino, T. (2022) Decreases of Ethanolamine Plasmalogen and Phosphatidylcholine in Erythrocyte Are a Common Phenomenon in Alzheimer's, Parkinson's, and Coronary Artery Diseases. *Brain Research Bulletin*, **189**, 5-10. https://doi.org/10.1016/j.brainresbull.2022.08.009

[6] Yamashita, S., Kiko, T., Fujiwara, H., Hashimoto, M., Nakagawa, K., Kinoshita, M., *et al.* (2016) Alterations in the Levels of Amyloid-β, Phospholipid Hydroperoxide, and Plasmalogen in the Blood of Patients with Alzheimer's Disease: Possible Interactions between Amyloid-β and These Lipids. *Journal of Alzheimer's Disease*, **50**, 527-537. https://doi.org/10.3233/jad-150640

[7] Abe, Y., Honsho, M., Nakanishi, H., Taguchi, R. and Fujiki, Y. (2014) Very-Long-chain Polyunsaturated Fatty Acids Accumulate in Phosphatidylcholine of Fibroblasts from Patients with Zellweger Syndrome and Acyl-CoA Oxidase1 Deficiency. *Biochimica et Biophysica Acta* (*BBA*)—*Molecular and Cell Biology of Lipids*, **1841**, 610-619. https://doi.org/10.1016/j.bbalip.2014.01.001

[8] Hossain, M.S., Ifuku, M., Take, S., Kawamura, J., Miake, K. and Katafuchi, T. (2013) Plasmalogens Rescue Neuronal Cell Death through an Activation of AKT and ERK Survival Signaling. *PLOS ONE*, **8**, e83508. https://doi.org/10.1371/journal.pone.0083508

[9] Ifuku, M., Katafuchi, T., Mawatari, S., Noda, M., Miake, K., Sugiyama, M., *et al.* (2012) Anti-Inflammatory/Anti-Amyloidogenic Effects of Plasmalogens in Lipopolysaccharide-Induced Neuroinflammation in Adult Mice. *Journal of Neuroinflammation*, **9**, Article No. 197. https://doi.org/10.1186/1742-2094-9-197

[10] Yamashita, S., Hashimoto, M., Haque, A.M., Nakagawa, K., Kinoshita, M., Shido, O., *et al.* (2017) Oral Administration of Ethanolamine Glycerophospholipid Containing a High Level of Plasmalogen Improves Memory Impairment in Amyloid β-Infused Rats. *Lipids*, **52**, 575-585. https://doi.org/10.1007/s11745-017-4260-3

[11] Fujino, T., Yamada, T., Asada, T., Tsuboi, Y., Wakana, C., Mawatari, S., *et al.* (2017) Efficacy and Blood Plasmalogen Changes by Oral Administration of Plasmalogen in Patients with Mild Alzheimer's Disease and Mild Cognitive Impairment: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. *EBioMedicine*, **17**, 199-205. https://doi.org/10.1016/j.ebiom.2017.02.012

[12] Obo, T., Obo, M., Fukuchi, M., Sasuga, Y., Fujino, T. and Kono, S. (2023) Orally Administered Plasmalogens Alleviate Psycho-Behavioral Parameters in Patients with Depressive Disorder: An Observational Study. *MJCR*, 1-14.

[13] Lewis, J.E. and Fravel, L.A. (2023) The Effects of HSOP on Cognition, Depression, and Activities of Daily Living in Older Adults with Cognitive Issues. *Integrative Medicine: A Clinician's Journal*, **21**, 16-20.

[14] Sugawara, T., Furuhashi, T., Shibata, K., Abe, M., Kikuchi, K., Arai, M., *et al.* (2019) Fermented Product of Rice with *Lactobacillus kefiranofaciens* Induces Anti-Aging Effects and Heat Stress Tolerance in Nematodes via Daf-16. *Bioscience, Biotechnology, and Biochemistry*, **83**, 1484-1489. https://doi.org/10.1080/09168451.2019.1606696

[15] Sugawara, T. and Sakamoto, K. (2020) Quercetin Enhances Motility in Aged and Heat-Stressed *Caenorhabditis elegans* Nematodes by Modulating Both HSF-1 Activity, and Insulin-Like and p38-MAPK Signalling. *PLOS ONE*, **15**, e0238528. https://doi.org/10.1371/journal.pone.0238528

[16] Yan, Z., Feng, J., Fienberg, A.A. and Greengard, P. (1999) D_2 Dopamine Receptors Induce Mitogen-Activated Protein Kinase and Camp Response Element-Binding Protein Phosphorylation in Neurons. *Proceedings of the National Academy of Sciences of the United States of America*, **96**, 11607-11612. https://doi.org/10.1073/pnas.96.20.11607

[17] Jiang, Y., Gaur, U., Cao, Z., Hou, S. and Zheng, W. (2022) Dopamine D1- and D2-Like Receptors Oppositely Regulate Lifespan via a Dietary Restriction Mechanism in *Caenorhabditis elegans*. *BMC Biology*, **20**, Article No. 71. https://doi.org/10.1186/s12915-022-01272-9

[18] Murakami, H. and Murakami, S. (2007) Serotonin Receptors Antagonistically Modulate *Caenorhabditis elegans* Longevity. *Aging Cell*, **6**, 483-488. https://doi.org/10.1111/j.1474-9726.2007.00303.x

[19] Somuah-Asante, S. and Sakamoto, K. (2022) Stress Buffering and Longevity Effects of Amber Extract on *Caenorhabditis elegans* (C. Elegans). *Molecules*, **27**, Article 3858. https://doi.org/10.3390/molecules27123858

[20] Yasuda, K. and Sakamoto, K. (2019) Oxytocin Promotes Heat Stress Tolerance via Insulin Signals in *Caenorhabditis elegans*. *Bioscience, Biotechnology, and Biochemistry*, **83**, 1858-1866. https://doi.org/10.1080/09168451.2019.1630253

[21] Speranza, L., di Porzio, U., Viggiano, D., de Donato, A. and Volpicelli, F. (2021) Dopamine: The Neuromodulator of Long-Term Synaptic Plasticity, Reward and Movement Control. *Cells*, **10**, Article 735. https://doi.org/10.3390/cells10040735

[22] Frouni, I., Kwan, C., Belliveau, S. and Huot, P. (2022) Cognition and Serotonin in Parkinson's Disease. *Progress in Brain Research*, **269**, 373-403. https://doi.org/10.1016/bs.pbr.2022.01.013

[23] Mitre, M., Minder, J., Morina, E.X., Chao, M.V. and Froemke, R.C. (2017) Oxytocin Modulation of Neural Circuits. In: Hurlemann, R. and Grinevich, V., Eds., *Behavioral Pharmacology of Neuropeptides: Oxytocin*, Springer, 31-53. https://doi.org/10.1007/7854_2017_7