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Orally Administered Plasmalogens Alleviate Psycho-behavioral Parameters in Patients with Depressive Disorder: An Observational Study

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Abstract

We report an observational study showing that the ingestion of scallop-derived plasmalogens (sPLS) supplement improved psycho-behavioral symptoms (anxiety, mood/emotion, and sleep feeling) in patients with depressive disorder. The study participants were 17 patients aged 40–70 years with major depressive disorder (n = 11) or persistent depressive disorder (n = 6) who started sPLS supplement in addition to the usual treatment. During the 3 months of the supplementation, the State-Trait Anxiety Inventory, self-check of fatigue, visual analog scale of 6-item mood/emotion (tension, depression, anger, vigor, fatigue, and confusion), and Oguri-Shirakawa-Azumi sleep inventory middle age and aged version were administered monthly. The state anxiety and trait anxiety scores statistically significantly improved after the use of sPLS. The physical and mental fatigue, mood and emotion scales, and sleep feeling (sleepiness on rising and refreshing) also showed a significant improvement with sPLS. The use of sPLS may facilitate alleviating anxiety and mental peripheral symptoms in patients with depressive disorders. However, the findings were based on the comparison between pretreatment and posttreatment data, and further investigation is warranted on the beneficial effects of plasmalogens in patients with depressive disorder.

Keywords: Scallop-derived plasmalogen; Major depressive disorder; Persistent depressive disorder; Anxiety

Introduction

Depression is a common mental disease that limits normal functioning and deteriorates the Quality of Life (QOL). In 2017, the prevalence of depressive disorders, major depressive disorder and dysthymia combined, was estimated to be 3.5% worldwide, the depressive disorders being the third leading cause of the global disease burden **[1,2].** The lifetime prevalence rates were 14.6% in 10 high-income countries and 11.1% in the 8 low- to middle-income countries **[3].** Pharmacotherapy and psycho-behavioral therapy are the standards in the management of depressive disorder. Full recovery is rare, and the recurrence is common in major depressive disorder **[4].** Thus, food-derived supplements have been sought as an alternative way of ameliorating depressive symptoms **[5-8].** Plasmalogens are a subclass of glycerophospholipids containing a vinyl ether bond at sn-1 position and are distributed in the brain and other tissues in humans. The homeostasis of plasmalogens is important for the functions of the central nervous system and vascular system **[9],** and much interest has been drawn to the beneficial effects of plasmalogens against Alzheimer's disease **[10,11].** Oral ingestion of Scallop-derived Plasmalogens (sPLS) has been reported to improve cognitive function in patients with Alzheimer's disease or mild cognitive impairment **[12-14].** Depression is extremely common in patients with Alzheimer's disease, with frequencies of 40–50% **[15-17].** In addition, common pathologies (hippocampal atrophy, changes in amyloid-β, and increased inflammatory cytokine levels) are present in both diseases **[18-20].** Thus, it is suggested that plasmalogens are also beneficial in patients with depressive disorder. Herein, we report an observational study showing that the ingestion of sPLS improved anxiety and other psycho-behavioral parameters in patients with major or persistent depressive disorder.

Materials and Methods

Study design and patients

The present study was based on the retrospective use of clinical data collected among patients who attended a mental clinic (Obo Clinic, Tokyo) in Japan. The use of an sPLS-containing supplement has been recommended to patients at the Clinic since May 2016. During the period from June 2018 to June 2019, four psycho-behavioral questionnaires had been administered to patients who started the sPLS supplement. A total of 39 patients answered the questionnaires and 18 patients were under medical treatment for major or persistent depressive disorder. The present study used the questionnaire data of 17 patients, excluding 1 patient who did not answer any of the follow-up questionnaires. The study protocol was approved by the Review Board of the BOOCS Clinic (Fukuoka, Japan, approval no.: 220818-1). All candidate patients (n = 18) were given the opportunity to decline the use of their clinical records for research. None of them declined the use of their data.

sPLS-containing capsule

One hard capsule contained 0.5 mg of sPLS (Plasmalogen S Hard Capsule, B&S Corporation Co., Ltd., Tokyo) and the recommended dosage was two capsules a day. The patients were asked to continue the supplement for at least 3 months.

Psycho-behavioral measurements

The patients answered the self-administered psycho-behavioral questionnaires before ingestion and every month thereafter for 3 months. The questionnaires included the State-Trait Anxiety Inventory (STAI) Form X

(Sankyobo, Kyoto, Japan) [21,22], physical and mental fatigue assessment form [23], Visual Analog Scale (VAS) of 6-item mood/emotion, and Oguri-Shirakawa-Azumi sleep inventory Middle Age and Aged version (OSA-MA) [24]. The STAI assesses state anxiety and trait anxiety each by 20 questions and each scale has scores from 20 to 80, with higher scores representing higher levels of anxiety. The trait anxiety of STAI contains two subscales: anxiety (T-anxiety) and depression (T-depression) [25]. The T-anxiety subscale consists of items 22, 28, 29, 31, 37, 38, and 40. The T-depression subscale consists of items 21, 23–27, 30, 32–36, and 39 [26]. The physical and mental fatigue scores ranged from 0 to 40 each, with higher scores indicating greater fatigue. The VAS mood/emotion was created for the present study with reference to the six subscales (tension, depression, anger, vigor, fatigue, and confusion) of the Profile of Mood States [27]. For each of the six items, a VAS of 100 mm in length was placed horizontally, with short vertical lines at both, ends and center. The left end was defined as "not at all (0)," and the right end was defined as "strong (10)." The current mood/emotion status was marked on the line and the length from the left end was measured in a unit of millimeter. The score of the vigor subscale was opposite to the scores of the other subscales and 100 minus the actual value was taken as negative vigor. The mean of the six-item scores was used as the overall score of mood/emotion. The mood/emotion scores ranged from 0 (minimum) to 100 (maximum), with higher scores indicating stronger emotion. The OSA-MA had 16 items to be answered at the time of waking up, and the participant selected one of the four options for each question. The OSA-MA consisted of five factors (sleepiness on rising, initiation and maintenance of sleep, frequent dreaming, refreshing, and sleep length), and the scores were calculated as corrected Zc score according to the scale value of Yamamoto et al. [24], with higher scores indicating better sleep quality.

Statistical analysis

Statistical analysis was performed with data from all patients who had both baseline and follow-up measurements for at least one outcome item. Some of the patients had missing information at different points of follow-up and for different outcome items. As for descriptive statistics, mean and Standard Deviation (SD) were used for continuous variables. The between-month variation was examined using Friedman's test with the last observation carried forward method for missing values. Multiple comparisons between each month and baseline were performed using the Nemenyi post hoc test. A mixed-effects model repeated-measures analysis was used for the assessment of the time course in the change during treatment from the baseline of an outcome parameter (dependent variable). The model included a fixed effect of the month and a random effect of the patient. The month of visit was treated as a categorical variable and an unstructured variance-covariance matrix was used. The marginal means and 95% Confidence Intervals (CIs) were estimated. The Mann–Whitney U test was used for the between-group comparison with respect to antidepressant use. Statistical analysis was conducted using XLSTAT v2022.3.2 software (Addinsoft, Paris, France) and Stata Statistical Software Release 13 (StataCorp, College Station, TX). A two-sided p-value of <0.05 was considered statistically significant.

Results

The background characteristics of the 17 patients are summarized in **Table 1.** The study patients were largely women (n = 14) and mean age was 52.2 years of age (SD, 7.7 years). Morbidity conditions of primary concern were major depressive disorder (n = 11) and persistent depressive disorder (n = 6). The duration of the core symptoms ranged from 0.8 to 22 years, with a median of 3.0 years **(Figure 1),** and 16 patients had attended the

clinic for at least 1 year. Nine patients (52.9%) were under medication for depressive disorder.

Table 1: Background characteristics of the study patients.

Characteristic	Value
Women, n (%)	14 (82.4)
Age in years, mean ± SD	51.2 ± 9.3
Height (cm), mean ± SD	161.6 ± 6.8
Weight (kg), mean ± SD	57.6 ± 11.2
Current smoking, n (%)	1 (5.9)
Alcohol use (≥1/week), n (%)	6 (35.3)
Major depressive disorder, n (%)	11 (64.7)
Persistent depressive disorder, n (%)	6 (35.3)
Disease duration (year), median (IQR)	3.0 (2.0–5.0)
Antidepressant medication, n (%)	9 (52.9)

IQR: Interquartile Range; SD; Standard Deviation.

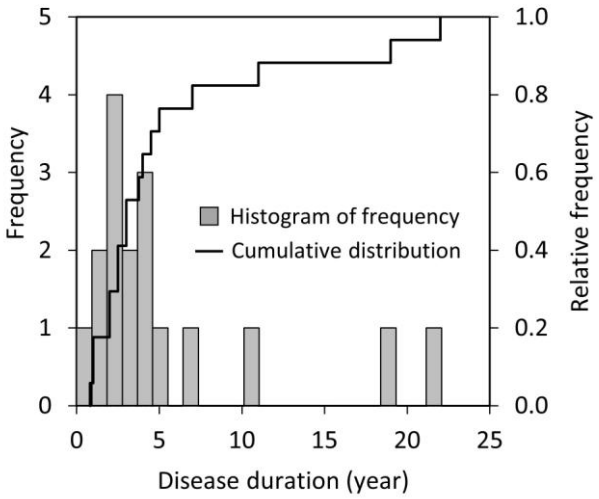

Figure 1: Histogram depicting the distribution of disease duration among the study patients.

The means and SD of the psycho-behavioral measurements according to months of treatment are summarized in **Table 2.** At baseline, the STAI scores were over 50 points for both state anxiety and trait anxiety, which exceeded the cutoff values (state anxiety, ≥41 in men and ≥42 in women; trait anxiety, ≥44 in men and ≥45 in women) **[21].** The baseline scores in the fatigue assessment form were also high in both physical fatigue and mental fatigue, which exceeded the cutoff values (physical fatigue, ≥12 in men and ≥14 in women; mental fatigue, ≥13 in men and ≥16 in women) **[23].** Regarding the mood/emotion, the mean scores of the subscales and average exceeded the midpoint (score, 50) by 10–15 points, except for the subscale of anger.

Table 2: Mean (SD) of psycho-behavioral measurements by month of treatment.

Parameter (score range)	Number†	Month				Freidman
		Baseline	1	2	3	p-value
STAI						
State anxiety (20–80)	16/16/14/14	53.0 (11.6)	51.8 (13.3)	48.3 (8.6)	43.6** (10.4)	0.007
Trait anxiety (20–80)	15/15/13/13	61.8 (11.4)	53.2** (10.7)	54.1 (10.8)	47.8*** (11.7)	$<10^{-4}$
T-anxiety (7–28)	15/15/13/13	23.7 (8.7)	19.3 (4.8)	19.2 (7.8)	16.6* (7.1)	0.01
T-depression (13–52)	15/15/13/13	38.1 (8.9)	34.7* (7.7)	34.6 (14.4)	31.4** (13.3)	0.001
Fatigue						
Physical (0–40)	17/16/15/15	14.0 (4.7)	9.8 (5.4)	8.9* (5.6)	7.0*** (5.0)	$<10^{-4}$
Mental (0–40)	17/16/14/15	22.6 (6.8)	16.6 (7.7)	16.6 (8.6)	12.6*** (7.9)	$<10^{-4}$
Total	17/16/14/15	36.6 (10.0)	26.4 (12.5)	25.8 (13.9)	19.6*** (12.3)	$<10^{-4}$
VAS mood/emotion						
Tension (0–100)	17/17/15/15	57.5 (29.7)	46.9 (24.1)	46.5 (22.5)	34.3 (20.9)	0.11
Depression (0–100)	17/17/15/15	58.3 (27.6)	56.8 (26.4)	54.2 (20.6)	37.7 (25.3)	0.08
Anger (0–100)	17/17/15/15	49.9 (28.8)	39.3 (29.5)	39.8 (25.5)	33.3 (22.7)	0.07
Vigor, inverted (0–100)	17/17/15/15	71.4 (22.1)	60.1* (22.3)	53.5*** (24.2)	50.5** (26.4)	$<10^{-4}$
Fatigue (0–100)	17/17/15/15	66.4 (24.1)	53.8 (25.4)	51.6 (26.6)	40.2* (31.1)	0.04
Confusion (0–100)	17/17/15/15	66.1 (32.4)	48.4 (26.1)	56.1 (21.1)	39.9** (22.8)	0.002
Average	17/17/15/15	61.6 (16.9)	50.9 (16.3)	50.3 (16.7)	39.3** (17.0)	0.009
Sleep OSA-MA‡						
Factor 1 (0–32.3)	16/15/14/13	9.5 (6.8)	12.6 (6.3)	14.9** (6.9)	16.4*** (7.8)	0.001
Factor 2 (0–29.6)	16/15/14/13	12.7	15.1	15.4	17.2	0.75

		(8.6)	(7.6)	(7.0)	(7.3)	
Factor 3 (0–29.5)	16/15/14/13	22.7 (9.1)	19.1 (9.6)	23.3 (8.0)	21.5 (9.5)	0.15
Factor 4 (0–32.7)	16/15/14/13	11.0 (8.1)	14.4 (8.0)	17.9 (9.6)	19.1*** (6.3)	$<10^{-4}$
Factor 5 (0–33.5)	16/15/14/13	16.6 (6.7)	16.8 (7.6)	16.2 (7.3)	18.0 (9.1)	0.80
Average (0–32.4)	16/15/14/13	14.5 (4.8)	15.6 (4.1)	17.6 (3.9)	18.4* (4.9)	0.007

STAI: State-Trait Anxiety Inventory; VAS: Visual Analog Scale; OSA-MA: Oguri-Shirakawa-Azumi sleep inventory Middle Age and Aged version.

†Number of patients for whom data were available at baseline, month 1, month 2, and month 3.

‡Factors 1–5 represent sleepiness on rising, initiation and maintenance of sleep, frequent dreaming, refreshing, and sleep length, respectively.

The between-month variation was examined using Friedman's test with the Nemenyi post hoc test.

$^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$, compared with baseline.

A statistically significant decrease in the state anxiety score was observed only at 3 months of treatment, whereas the trait anxiety score began to significantly decrease at 1 month of treatment. At 3 months, the STAI score was <50 points for both state anxiety and trait anxiety. The trait anxiety subscales also showed significant improvement in both T-anxiety and T-depression at 3 months, and the latter also significantly improved at 1 month. Both physical fatigue and mental fatigue showed a substantial improvement at 3 months in terms of the magnitude of change and statistical significance. The mean VAS score of 6-item mood/emotion gradually improved and showed a significant improvement at 3 months. Of the six individual items, vigor, fatigue, and confusion showed the most evident improvement, whereas tension, depression, and anger showed no significant decrease in the score even at 3 months. Of the five factors of the Sleep OSA-MA, factors 1 (sleepiness on rising) and 4 (refreshing) showed a gradual improvement with the advance of treatment, resulting in a statistically significant improvement at 3 months.

The results in the mixed-effects model analysis are summarized in **Table 3.** The results were generally compatible with those shown in **Table 2.** The p-values for the overall difference represent the variation in the changes from the baseline at the 3 points in time and are not necessarily compatible with the p-values shown in Table 2, which were based on the 4-point variation. The 95% CI not including 0 represents a statistically significant change from the baseline. In the mixed-effects model analysis, the scores of physical fatigue, mental fatigue, and total fatigue each significantly decreased at early months of treatment.

Table 3: Average changes (95% confidence intervals) from baseline at 1, 2, and 3 months of treatment in psycho-behavioral measurements: mixed-model repeated-measures analysis.

Parameter (score range)	Number*	Month 1	Month 2	Month 3	p†
STAI					
State anxiety (20–80)	16/14/14	−1.3	−3.1	−8.1	0.006
		(−6.6, 4.1)	(−8.2, 2.0)	(−12.8, −3.4)	
Trait anxiety (20–80)	15/13/13	−8.6	−6.2	−12.3	0.003
		(−14.8, −2.4)	(−10.4, −1.9)	(−18.2, −6.5)	
T-anxiety (7–28)	15/13/13	−4.4	−3.7	−6.4	0.006
		(−8.5, −0.3)	(−7.9, 0.4)	(−10.3, −2.4)	
T-depression (13–52)	15/13/13	−3.4	−2.7	−5.9	0.02
		(−8.5, 1.7)	(−7.6, 2.2)	(−10.8, −1.1)	
Fatigue					
Physical (0–40)	16/15/15	−4.0	−4.9	−6.8	0.006
		(−6.3, −1.6)	(−6.7, −3.0)	(−8.8, −4.8)	
Mental (0–40)	16/14/15	−5.4	−6.2	−9.8	$<10^{-4}$
		(−9.6, −1.2)	(−10.0, −2.4)	(−13.5, −6.2)	
Total	16/14/15	−9.3	−11.1	−16.6	$<10^{-7}$
		(−15.5, −3.1)	(−16.3, −6.0)	(−21.0, −12.1)	
VAS mood/emotion					
Tension (0–100)	17/15/15	−10.6	−10.5	−23.2	0.06
		(−26.8, 5.5)	(−28.5, 7.5)	(−41.6, −4.8)	
Depression (0–100)	17/15/15	−1.5	−2.4	−19.0	0.01
		(−16.8, 13.8)	(−18.4, 13.5)	(−35.4, −2.6)	
Anger (0–100)	17/15/15	−10.6	−8.1	−14.7	0.63
		(−21.5, 0.4)	(−21.6, 5.4)	(−26.2, −3.1)	
Vigor, inverted (0–100)	17/15/15	−11.2	−20.0	−22.2	0.24
		(−22.2, −0.2)	(−31.7, −8.4)	(−34.1, −10.3)	
Fatigue (0–100)	17/15/15	−12.5	−13.7	−25.1	0.18
		(−24.1, −0.9)	(−29.6, 2.2)	(−42.5, −7.7)	
Confusion (0–100)	17/15/15	−17.6	−9.4	−26.0	$<10^{-4}$
		(−31.8, −3.5)	(−26.1, 7.3)	(−47. 0, −4.9)	
Average (0–100)	17/15/15	−10.7	−10.9	−22.3	0.01
		(−19.1, −2.3)	(−20.5, −1.4)	(−33.8, −10.7)	
Sleep OSA-MA‡					
Factor 1 (0–32.3)	15/14/13	3.2	5.2	6.1	0.14
		(0.4, 6.0)	(2.7, 7.7)	(2.0, 10.3)	
Factor 2 (0–29.6)	15/14/13	2.7	1.9	4.1	0.16

		(−2.3, 7.6)	(−3.8, 7.5)	(−1.2, 9.4)	
Factor 3 (0–29.5)	15/14/13	−4.0	0.2	−2.3	0.01
		(−7.2, −0.9)	(−3.6, 4.0)	(−7.3, 2.7)	
Factor 4 (0–32.7)	15/14/13	3.5	6.9	8.0	0.008
		(−1.3, 8.3)	(3.3, 10.5)	(4.0, 12.0)	
Factor 5 (0–33.5)	15/14/13	−0.4	−0.1	2.3	0.66
		(−4.7, 3.9)	(−2.8, 2.6)	(−2.4, 6.9)	
Average (0–31.5)	15/14/13	1.1	2.9	3.6	0.07
		(−1.4, 3.5)	(0.7, 5.1)	(0.8, 6.5)	

STAI: State-trait Anxiety Inventory; VAS: Visual Analog Scale; OSA-MA: Oguri-Shirakawa-Azumi sleep inventory Middle Age and Aged version.

*Number of patients for whom data were available at month 1, month 2, and month 3.

†p value for the overall difference among the 3 points of month.

‡Factors 1–5 represent sleepiness on rising, initiation and maintenance of sleep, frequent dreaming, refreshing, and sleep length, respectively.

The changes from the baseline at 3 months of treatment did not differ by antidepressant medication in most of the psycho-behavioral parameters. Only the VAS confusion showed a statistically significantly greater improvement in patients without antidepressant medication than in those with **(Table 4).** There were virtually no differences in the changes of the psycho-behavioral measurements with respect to the duration of depression. Regarding VAS tension, there was a statically significantly greater improvement in patients with durations of over 3 years than in those with ≤3 years **(Table 5).**

Table 4: Mean changes from baseline at 3 months of treatment in psycho-behavioral measurements according to antidepressant medication.

Parameter (score range)	Antidepressant (+)		Antidepressant (−)		p†
	n	Mean ± SD	n	Mean ± SD	
STAI					
State anxiety (20–80)	7	−7.1 ± 10.8	6	−8.2 ± 9.7	0.67
Trait anxiety (20–80)	7	−10.7 ± 7.3	6	−14.7 ± 17.2	0.77
T-anxiety (7–28)	7	−7.6 ± 9.3	6	−5.5 ± 8.1	0.47
T-depression (13–52)	7	−2.9 ± 11.0	6	−9.2 ± 9.2	0.77
Fatigue					
Physical (0–40)	8	−6.0 ± 4.4	7	−7.6 ± 3.8	0.56
Mental (0–40)	8	−6.3 ± 7.6	7	−12.9 ± 6.6	0.09
Total	8	−12.3 ± 7.1	7	−20.4 ± 9.6	0.11
VAS mood/emotion					
Tension (0–100)	8	−17.1 ± 46.7	7	−24.6 ± 33.3	0.60
Depression (0–100)	8	−15.3 ± 38.6	7	−20.1 ± 31.5	0.82

Anger (0–100)	8	−12.4 ± 28.6	7	−17.3 ± 18.4	0.32
Vigor, inverted (0–100)	8	−16.8 ± 31.3	7	−27.1 ± 12.8	0.35
Fatigue (0–100)	8	−21.0 ± 42.5	7	−32.0 ± 26.0	0.60
Confusion (0–100)	8	−5.1 ± 50.6	7	−45.1 ± 29.1	0.049
Average (0–100)	8	−14.6 ± 28.4	7	−27.7 ± 16.2	0.25
Sleep OSA-MA‡					
Factor 1 (0–32.3)	6	2.4 ± 9.1	7	9.1 ± 7.5	0.22
Factor 2 (0–29.6)	6	4.2 ± 14.5	7	7.4 ± 6.8	0.32
Factor 3 (0–29.5)	6	−1.9 ± 7.2	7	−3.7 ± 11.5	0.66
Factor 4 (0–32.7)	6	4.4 ± 4.0	7	10.1 ± 10.1	0.52
Factor 5 (0–33.5)	6	−1.8 ± 7.4	7	5.6 ± 9.3	0.22
Average (0–31.5)	6	1.4 ± 5.0	7	5.7 ± 6.2	0.20

STAI: State-trait Anxiety Inventory; VAS: Visual Analog Scale; OSA-MA: Oguri-Shirakawa-Azumi sleep inventory Middle Age and Aged version.

†p value based on Mann–Whitney *U* test.

‡Factors 1–5 represent sleepiness on rising, initiation and maintenance of sleep, frequent dreaming, refreshing, and sleep length, respectively.

Table 5: Mean changes from baseline at 3 months of treatment in psycho-behavioral measurements according to morbid duration.

Parameter (score range)	Duration ≤ 3 years		Duration > 3 years		p†
	n	Mean ± SD	n	Mean ± SD	
STAI					
State anxiety (20–80)	7	−3.6 ± 6.0	7	−11.6 ± 11.1	0.10
Trait anxiety (20–80)	6	−10.8 ± 10.3	7	−14.0 ± 14.6	0.72
T-anxiety (7–28)	6	−8.2 ± 10.4	7	−5.3 ± 7.0	0.47
T-depression (13–52)	6	−2.7 ± 12.8	7	−8.4 ± 7.6	0.32
Fatigue					
Physical (0–40)	8	−7.8 ± 3.7	7	−5.6 ± 4.4	0.38
Mental (0–40)	8	−9.3 ± 8.0	7	−9.4 ± 8.0	0.68
Total	8	−17.0 ± 9.1	7	−15.0 ± 9.7	0.64
VAS mood/emotion					
Tension (0–100)	8	0.0 ± 34.3	7	−44.1 ± 33.3	0.018
Depression (0–100)	8	−10.3 ± 35.6	7	−25.9 ± 33.4	0.49
Anger (0–100)	8	−14.5 ± 19.7	7	−14.9 ± 29.3	0.77
Vigor, inverted (0–100)	8	−19.3 ± 28.5	7	−24.3 ± 20.3	0.73
Fatigue (0–100)	8	−27.4 ± 36.0	7	−24.7 ± 36.6	0.52
Confusion (0–100)	8	−23.6 ± 45.0	7	−24.0 ± 49.6	1.00
Average (0–100)	8	−15.8 ± 25.6	7	−26.3 ± 21.9	0.49
Sleep OSA-MA‡					
Factor 1 (0–32.3)	7	3.8 ± 10.3	6	8.5 ± 6.1	0.28
Factor 2 (0–29.6)	7	3.8 ± 6.1	6	8.5 ± 14.5	0.78
Factor 3 (0–29.5)	7	−2.7 ± 12.2	6	−3.1 ± 5.9	1.00
Factor 4 (0–32.7)	7	9.0 ± 9.2	6	5.7 ± 7.2	0.48
Factor 5 (0–33.5)	7	5.4 ± 9.2	6	−1.7 ± 7.7	0.25
Average (0–31.5)	7	3.9 ± 6.8	6	3.6 ± 5.3	1.00

STAI: State-trait Anxiety Inventory; VAS: Visual Analog Scale; OSA-MA: Oguri-Shirakawa-Azumi sleep inventory Middle Age and Aged version.

†p value based on Mann–Whitney *U* test.

‡Factors 1–5 represent sleepiness on rising, initiation and maintenance of sleep, frequent dreaming, refreshing, and sleep length, respectively.

Discussion

The present study showed that the 3-month use of sPLS supplement resulted in substantial improvements in anxiety, fatigue, mood/emotion, and sleep in patients with major or persistent depressive disorder. Although the present study did not directly assess the severity of depression, the psycho-behavioral scales assessed are useful

measures for the assessment of the QOL in patients with depressive disorder. It should be noted that the T-depression score in the STAI trait anxiety showed a statistically significant decrease at 3 months **(Table 2 and 3).** The score for depression in the VAS mood/emotion assessment also statistically significantly improved at 3 months in the mixed-effects model analysis **(Table 3).** The observation without a control group may raise a serious concern on causality; however, most of the patients had a medical treatment for a fairly long period. Interestingly, the improvements in most parameters were similar in patients with and without antidepressant medication, whereas patients without antidepressant medication showed better improvement in confusion. Anxiety is a common, but not specific, symptom in depressive disorder. Approximately two-thirds of patients with major depression have a comorbid anxiety disorder. Importantly, comorbid anxiety is associated with poor prognosis with respect to remission, suicidal idealization, and other outcomes in patients with major depressive disorder **[28,29].** In this regard, the observed improvement in the anxiety scores with sPLS supplementation has an important clinical implication in the management of depressive disorders.

Various environmental and genetic factors have been implicated in the etiology of depressive disorders. Postulated pathophysiological mechanisms include the monoamine hypothesis, hypothalamic-pituitary-adrenal axis changes, inflammation, neuroplasticity, structural and functional brain changes, and epigenetics, as reviewed in detail elsewhere **[4].** Of these, neuroinflammation and neuroplasticity are of particular relevance to the effects of sPLS. *In vivo* and *in vitro* studies have consistently shown that inflammatory stimuli decrease the levels of plasmalogens in the brain and neural cell lines and that the administration of plasmalogens inhibits the inflammatory processes in the brain tissue **[30-33].** As for neurogenesis, Brain-Derived Neurotropic Factor (BDNF) seems to play an important role in the development of depression **[34,35].** Although serum BDNF is diminished in patients with major depressive disorder, the reduced BDNF can be restored with antidepressant treatment **[36].** The administration of antidepressants enhances the expression of BDNF through the phosphorylation of cyclic adenosine monophosphate response element binding protein (CREB) in neurons **[37,38].** It is of particular interest that the ingestion of plasmalogens induced BDNF expression via phosphorylation of CREB in the mouse brain **[39].** Furthermore, a recent randomized trial showed that plasmalogen ingestion alleviated negative mood states in healthy young men **[40].**

Conclusion

The use of plasmalogens alleviated anxiety, fatigue, mood/emotion, and sleep in patients with major or persistent depressive disorder. Although the findings were based on the comparison between pretreatment and posttreatment data, further investigation is warranted on the beneficial effects of plasmalogens in patients with depressive disorder.

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