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Clinical Trial to Evaluate if Balenine, A Major Component of Whale Meat Extract, Improves Cognitive Function in Subjects with Symptoms of Increasing Forgetfulness

Takahiro Hirabayashi[1], Junko Shibato[1], Ai Kimura[1], Michio Yamashita[2], Fumiko Takenoya[2*] and Seiji Shioda[3*]

[1]*Clinical Medicine Research Laboratory, Shonan University of Medical Sciences, Japan*

[2]*Department of Sports Sciences, School of Pharmacy, Hoshi University, Japan*

[3]*Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Shonan University of Medical Sciences, Japan*

***Corresponding author:** Seiji Shioda, Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Shonan University of Medical Sciences, 16-48, Kamishinano, Totsuka-ku, Yokohama, Kanagawa 244-0806, Japan

Fumiko Takenoya, Department of Sports Sciences, School of Pharmacy, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo, 142-8501, Japan.

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ABSTRACT

Background: Balenine (beta-alanyl-N tau-methyl histidine), an imidazole dipeptide reported to have antioxidant and anti-fatigue effects in animal models and humans, is present in abundant amounts in whale meat. Previously, we reported that long-term consumption of whale meat extracts containing balenine improve cognitive function in a mouse model of Alzheimer's disease. To test whether this cognition-improving effect of balenine can also be observed in humans, we conducted a double-blind clinical trial in subjects with symptoms of increasing forgetfulness.

Methods: This study was a randomized, placebo-controlled, double-blind study. We recruited men and women aged 60 to 79 who felt that levels of forgetfulness had increased as a subjective symptom. Fourteen subjects were allocated into two groups, and one group received balenine and the other placebo, both of which were given in capsule form for 12 weeks. We performed the Mini Mental State Examination (MMSE), MCI screening, Zung self-rating depression scale (SDS), Uchida-Kraepelin test and assay for antioxidative potential and cortisol in saliva after the 6-week and 12-week consumption of capsules.

Results: There were no significant changes in the MMSE, MCI screening between the two groups. Results on balenine- and placebo-treated subjects showed that the group taking balenine for 12 weeks tended to show reduced levels of depression compared to the placebo group. Uchida-Kraepelin test results showed that the 12-week balenine treatment significantly improved cognitive function, work efficiency and concentration compared to placebo. In addition, salivary cortisol, a biomarker of psychological stress, tended to be lower in the balenine treatment group compared to the placebo group, although differences were not statistically significant.

Conclusions: Long-term consumption of whale meat extract containing balenine may reduce the effects of dementia or inhibit its progression of dementia by reducing psychological stress in humans.

Keywords: Balenine; Cognitive Function; Dementia; Depression; Imidazole Dipeptide; Psychological Stress

Abbreviations: SDS: Self-Rating Depression Scale; ROS: Reactive Oxygen Species; SAMP8: Senescence-Accelerated Mouse Prone 8; MMSE: Mini-Mental State Examination; BAP: Biological Antioxidant Potential

Introduction

According to a Japanese Ministry of Health and Welfare report in 2015, it is estimated that the number of dementia patients in Japan will exceed 7 million in 2025 and 10 million in 2050, meaning that one out of every five elderly people over the age of 65 will suffer from dementia. Drug development to treat and prevent dementia, including Alzheimer's disease, is being actively pursued around the world, but there is still no fundamental cure for the disease. While several anti-dementia drugs, including donepezil hydrochloride, galantamine, rivastigmine and memantine hydrochloride have been approved and are being used for the treatment of Alzheimer's disease, we believe, nevertheless, that a role also exists for the use of long-term non-drug therapies to attenuate the progression of dementia. Balenine (beta-alanyl-N tau-methyl histidine) is an imidazole dipeptide and a major component of whale meat. Several reports on the physiological effects of imidazole dipeptides including balenine have been reported in the literature [1,2]. Oxidative stress occurs when the production of reactive oxygen species (ROS) in the body is not matched by their removal by endogenous antioxidant systems (antioxidant compounds and antioxidant enzymes) [3,4]. When the state of high oxidative stress is long- lasting, DNA, proteins, lipids (including cell membranes), and carbohydrates in the body undergo oxidative damage, and nitric oxide synthesis may induce ongoing pathological diseases [5].

We previously reported that whale meat contains many antioxidant substances, one of which is balenine [6]. Moreover, studies aimed at attenuating high workload-induced fatigue in humans [7] and improving muscle endurance in mice [8] revealed that balenine suppresses systemic fatigue. Further to this, we reported that dementia symptoms are improved when senescence-accelerated mouse prone 8 (SAMP8) mice, the most commonly used mouse model of dementia, ingest whale meat extract containing balenine. Experimental behavior results showed that long-term, continuous administration of balenine improves short- and long-term memory function in animal experiments using SAMP8 mice [6], which may provide some insights on its possible benefits in humans. If an effect of balenine on dementia in humans can be shown, this could be expected to reduce the burden on patients and their caregivers and lead to a reduction in national healthcare expenses. To this end, we have conducted a clinical trial on persons with symptoms of forgetfulness to evaluate whether treatment with whale meat extract containing balenine will improve dementia-like symptoms compared to a matched cohort treated with placebo.

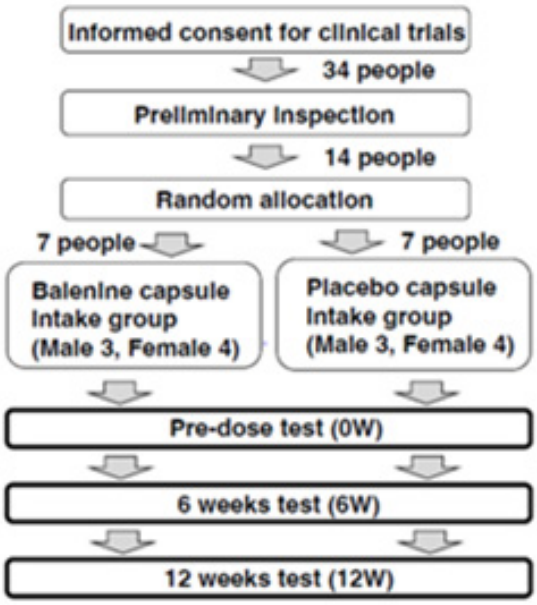

Figure 1A

	Pre-dose test (0W)	6 weeks test (6W)	12 weeks test (12W)
MMSE	○	○	○
MCI screening	○		○
Zung self-rating depression scale	○	○	○
Uchida-Kraepelin test	○	○	○
Saliva collection (BAP, Quantification of cortisol)	○	○	○

Figure 1B

Figure 1: Study outline.

A. Outline of clinical trial and inclusion of study participants. Fourteen participants were selected from 34 candidates aged 60-79 years who provided their consent to participate in the study. Subjects were divided into two groups (balenine treatment group, placebo group) of 7 participants each.

B. Tests performed at baseline (pre-treatment; W0), and at the 6- (W6) and 12-week (12W) timepoints.

Methods

Subjects and Study Design

This study was a randomized, placebo-controlled, double-blind study. We recruited men and women aged 60 to 79 who felt that levels of forgetfulness had increased as a subjective symptom. Thirty-four candidates provided their informed consent to participate. Following Mini-Mental State Examination (MMSE) [9] and preliminary examinations (interview, physical measurements, physiological examination, infectious disease examination), 14 of the 34 candidates (6 males, 8 females) were selected to enter the study. These 14 subjects were allocated into two groups by block randomization so that age and gender were distributed as evenly as possible between the groups. One group received balenine and the other placebo, both of which were given in capsule form. After the pre-dose baseline testing (W0) described above, the subjects took 5 capsules of either balenine or placebo 3 times daily (after each meal) for 12 weeks, and examinations were repeated after 6 weeks (W6) and at end-of-study (12 weeks, W12) from the start of ingestion the capsules. The study design and tests carried out at each time-point are shown in Figures 1A & 1B, respectively. Data collection for all baseline and in-study tests including blood collection were conducted at Chiyoda Paramedical Care Clinic (Tokyo, Japan). This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the Ethics Committee at Hoshi University (approval number: 29-013) and Chiyoda Paramedical Care Clinic (Tokyo, Japan, approval number: SLS17C1). Written informed consent was obtained from all subjects. The study was registered in the UMIN Clinical Trials Registry (UMIN000031366).

Balenine and Placebo Capsules

Whale meat extract (Whale Extract B8, Kyodo Senpaku Co. Ltd., Tokyo, Japan) containing balenine was enclosed in porcine-derived gelatin capsules, the contents of which are shown in Table 1. Subjects in the balenine treatment group consumed 2.5 g of whale meat extract containing 195 mg of balenine per day. Placebo capsules were packaged with corn starch in place of the whale meat extract. Calcium stearate was added to all capsules as a lubricant, and finely divided silicon dioxide was added as an anti- caking agent.

Table 1: Compositions of balenine- and placebo-containing capsules.

	Balenine capsules	Placebo capsules
Whale extract	166.7	0
(Balenine)	(13.0)	(0.0)
Corn starch	49.3	216.0
Calcium stearate	2.0	2.0
Silicon dioxide powder	2.0	2.0
		mg / capsule

Note: Contents were packaged in porcine-derived gelatin capsules. Corn starch was used in placebo capsules in place of whale meat extract.

Mini Mental State Examination (MMSE)

The MMSE is a tool that is used widely to assess mental status via the evaluation of cognitive function, including orientation, registration, attention and calculation, recall, and language [9]. The maximum score for the MMSE is 30, with scores of 24-27 possibly indicating MCI, and scores of 23 or lower indicative of cognitive impairment. In this study, we used the Japanese version of MMSE (MMSE-J).

MCI Screening

The MCI Screen is a brief neuropsychological test where the risk of MCI is evaluated by quantifying specific proteins (ApoA1, C3, TTR) in the blood. Statistical analysis of the results provides four possible grades – A to D – relating to the absence or presence of cognitive impairment (A: Healthy; B: Risk of cognitive impairment is low, but it is necessary to improve lifestyle habits; C: Risk of cognitive impairment is moderate, with diagnosis by a specialist recommended if necessary; D: Risk of cognitive impairment is high, with detailed tests by a specialist recommended to facilitate diagnosis) [10,11]. Whole blood samples were taken from subjects in each group at W0 and W12, and used for the testing.

Zung Self-Rating Depression Scale (SDS)

The Zung SDS is a questionnaire-based test in which subjects provide answers that enable their depressive state to be evaluated. The questionnaire consists of 20 items, where the degree to which the item can be answered in the affirmative is provided according to one of 4 levels (always, considerably, occasionally, very occasionally). The SDS score is evaluated over a range of 20 to 80 points, with the trend for depression and the score being positively correlated (i.e. when the depression tendency is high, the score increases) [12].

Uchida-Kraepelin Test

The Uchida-Kraepelin test is a questionnaire modified from Kraepelin's arithmetic test, which was originally developed by Y. Uchida, and is an assessment of cognitive function, work efficiency and concentration [13]. Subjects are asked to calculate the sum of random, single-digit numbers printed on a horizontal line; this is done for one minute per line, with the line changed every minute over 5 consecutive minutes. This task causes mental stress/fatigue and therefore provides a measure of cognitive function, work efficiency and concentration, which can be evaluated from the number of responses completed over the 5-minute period.

Assay for Anti-Oxidative Potential and Cortisol in Saliva

Saliva was collected from subjects via a saliva collection tube (Salivette, Salimetrics,Inc.). The saliva was centrifuged at 3,000 x g for 10 min to remove debris, and the resulting supernatant used to provide samples for assays as described in the following. The anti-oxidative potential of saliva collected from subjects was measured with a commercial kit (Biological antioxidant potential (BAP) test)

using an automatic analyzer (FREE Carrio Duo; Diacron International, Italy) according to the manufacturer's instructions with minor modifications. Briefly, saliva aliquots were mixed with reactive solutions and the absorbance determined at 510 nm immediately prior to initiation of the reaction. The mixture was then incubated for 5 min at 37 ºC, and the post-reaction absorbance of the mixture was measured as previously described [4,14]. Cortisol levels in samples were also quantified; this was performed using the Cortisol EIA Kit, Expanded Range, High Sensitivity, Salivary (Funakoshi Co., Ltd.).

Statistical Analysis

The results were expressed as mean ± standard error of the mean (S. E. M.). Statistical significances within groups were analyzed by one- and two-way analysis of variance (ANOVA) followed by the Bonferroni multiple comparisons test. P-values less than 0.05 ($P<0.05$) were considered significant.

Results

Subject Profiles

The gender profile, and mean age and MMSE score at the preliminary examination (baseline; W0) of subjects in each study group (balenine treatment group, placebo group) are shown in Table 2. Each group consisted of 3 males and 4 females, with average ages of 73.0 years for the balenine treatment group and 73.3 years for the placebo. There were no significant differences in age or MMSE scores between the two groups. Treatment coherence (percentage of capsules taken as required) during the trial was sufficiently high as to have had no effect on the study outcome (balenine group 99.8%, placebo group 99.5%).

Table 2: Baseline characteristics of study subjects.

	Balenine treatment group	Placebo group	
Number of subjects	7	7	
Gender	3 males, 4 females	3 males, 4 females	
Age mean + SD	73.0 ± 2.8	73.3 ± 2.4	(p = 0.445)
MMSE score mean + SD	27.9 ± 1.1	28.4 ± 1.2	(p = 0.229)

Effect of Balenine Intake on Measured MMSE Scores

The MMSE score (maximum score 30) for each group at each time-point is shown in Figure 2. Increased scores were observed in the treatment and placebo groups compared to baseline (W0) at both W6 and W12, but the changes were not statistically significant over time or between the groups. While improved cognitive function as per the MMSE score was observed in both groups, these findings suggest that balenine was not superior to placebo following 12 weeks of treatment.

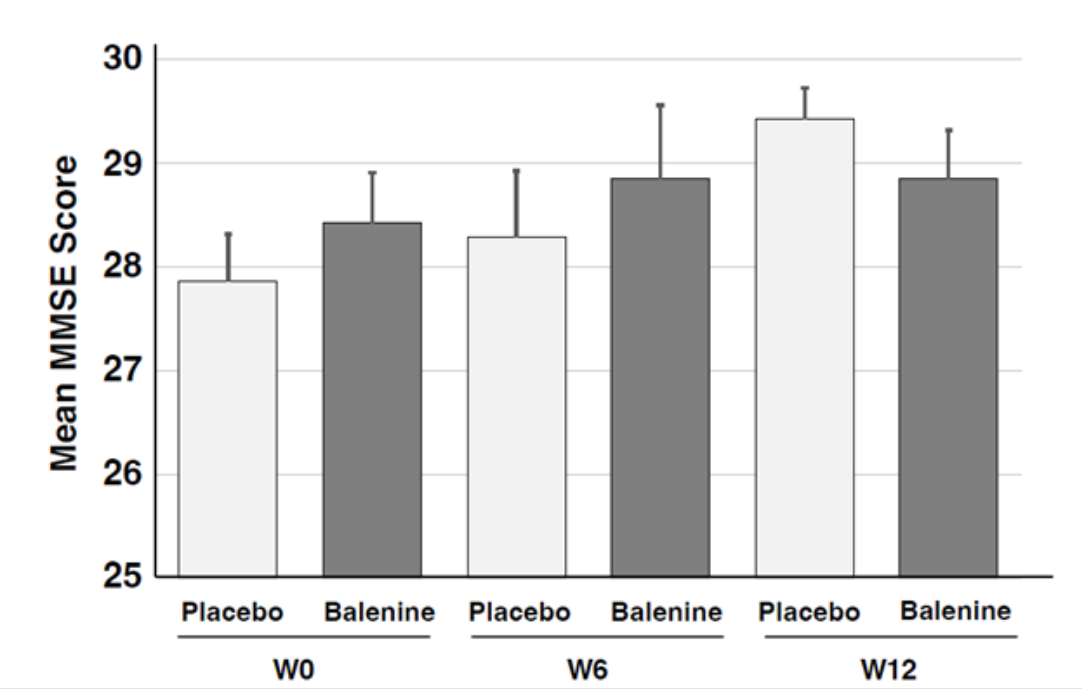

Figure 2: Effect of balenine intake on MMSE score.

Note: MMSE scores at baseline (W0), 6 weeks (W6) and 12 weeks (W12). Values are expressed as the mean + SEM.

Effects of Balenine Intake on MCI

Changes in MCI screening scores (grades A to D) at W12 are shown in Figure 3 with respect to baseline (W0). Here, improvements of one step (for example, from D to C) were given a value of «+1», whereas worsening by one step (for example, from B to C) was set to «-1 (Figure 3A). In this way, MCI scores improved in both groups from baseline to W12, but the differences were not statistically significant (Figure 3B). When changes in MCI screening scores were evaluated by gender, balenine-treated male subjects exhibited a statistically significant improvement from baseline to W12, although there was no statistically significant difference compared with the placebo group. On the other hand, in female subjects, a tendency towards improvement was seen in both groups but the improvement in balenine-treated patients from baseline to W12 was not significant (Figure 3C). Taking into account the small cohort sizes, these results could infer that the ingestion of balenine over a prolonged time course might be effective in improving cognitive function, particularly in male subjects.

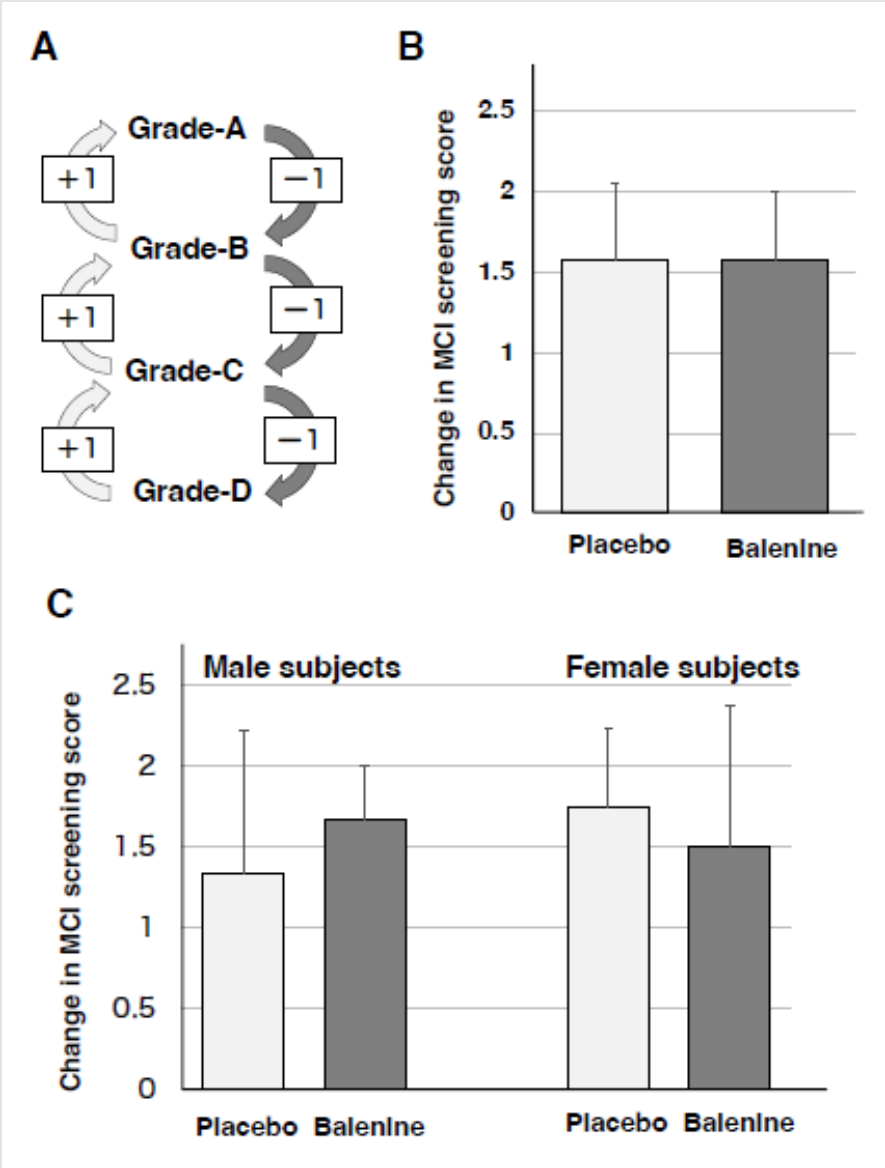

Figure 3: Effect of balenine intake on mild cognitive impairment.

A. Results of MCI screening were rated as "+1" for a one-step improvement and "-1" for a one-step worsening compared to the screening score at baseline. Changes of MCI scores for all participants

B. And by gender

C. At 12 weeks. Values are expressed as the mean + SEM.

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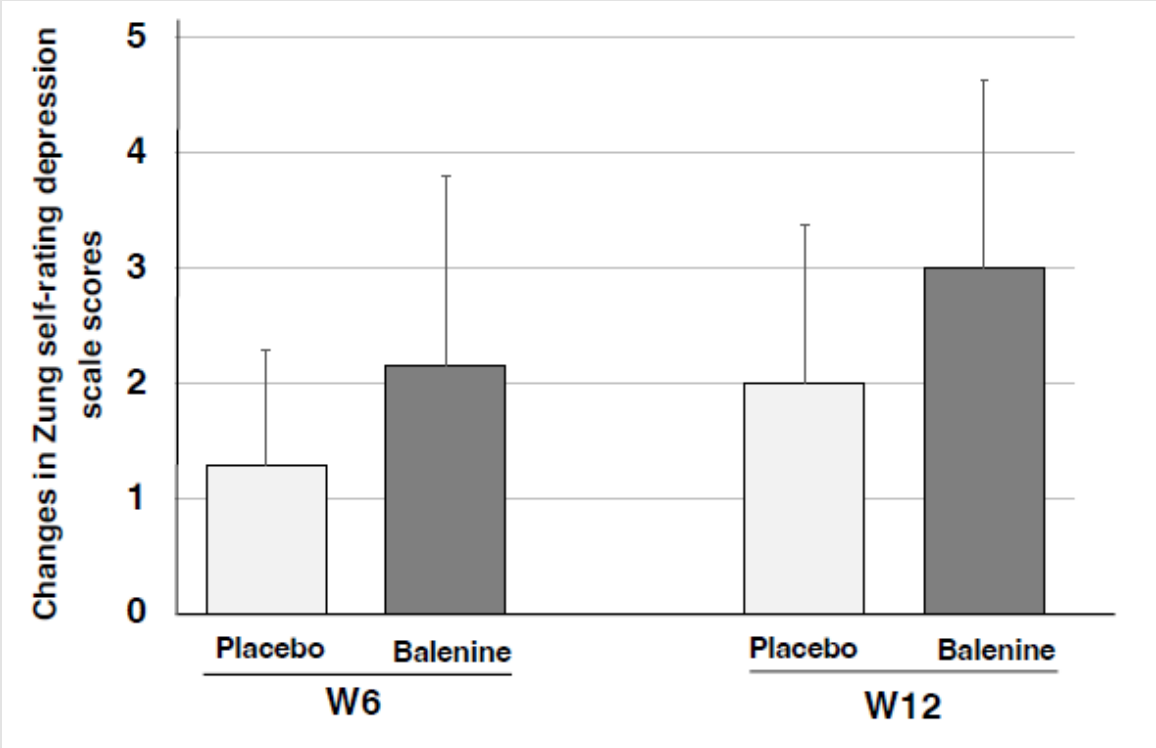

Figure 4: Effect of balenine intake on depression scores.

Note: The number of points by which the score at baseline decreased is shown as an improvement score. Values are expressed as the mean + SEM.

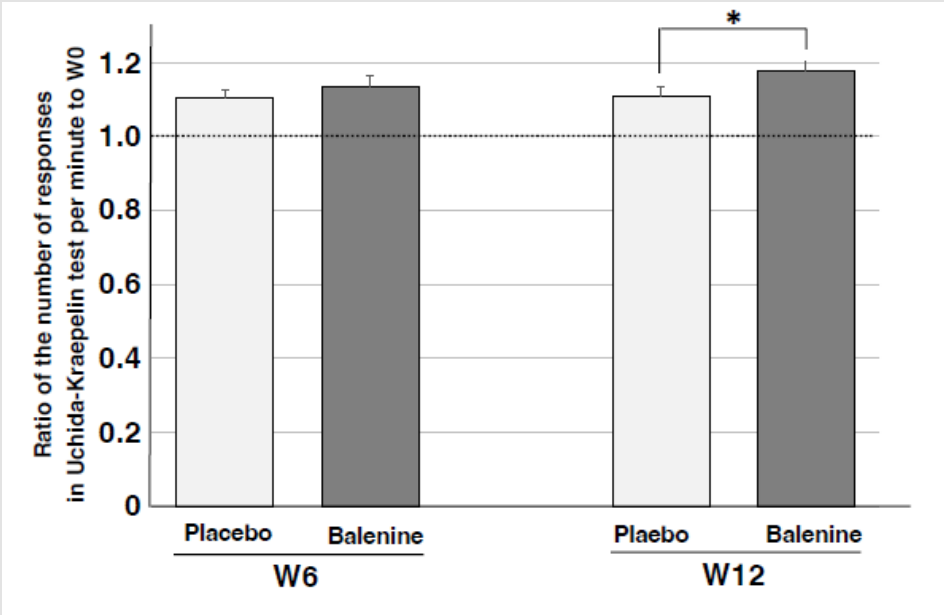

Figure 5: Effect of balenine intake on cognitive function, work efficiency and concentration.

Note: Ratio of the number of Uchida-Kraepelin test responses per minute at 6 weeks (W6) and 12 weeks (W12) compared to baseline (0W). Values are expressed as the mean + SEM. *$p < 0.05$.

Balenine Intake Tends to Decrease Depression

Since the association between dementia and depression has long been known [15], we also analyzed the antidepressant effect of balenine by using the Zung self-rating depression scale (SDS). SDS scores at W6 and W12 of balenine intake were compared with those at baseline (W0), and against the placebo groups (Figure 4). Trends towards improvement were observed for both groups at W6 and W12. In addition, balenine treatment resulted in greater improvements compared to those seen with placebo, although these differences were not statistically significant. These results indicate that the ingestion of balenine may improve the depressive state in some patients. Intake of balenine may improve cognitive function, work efficiency and concentration. The effects of balenine intake on cognitive function, work efficiency and concentration were measured by applying the Uchida-Kraepelin test. When the number of responses per minute at W6 and W12 was compared against baseline values, increases were seen in both the balenine-treated and placebo groups, with this effect being statistically significant at W12 (Figure 5). These results suggest that the intake of balenine may improve cognitive function, work efficiency and concentration in older individuals with symptoms of increased forgetfulness.

Long-Term Intake of Balenine Reduces Psychological Stress

The BAP test provides an indication of the level of antioxidant substances in samples, which in turn is considered to be correlated with anti-stress activity. As such, BAP tests are used widely to assess the oxidative/antioxidative states both in basic research and clinical studies, and their usefulness has been widely reported [16]. In this study, BAP was measured using saliva samples collected from subjects (see Materials & Methods). BAP values at W6 and W12 were expressed as a ratio of baseline values prior to balenine/placebo treatment onset. BAP ratios increased at both W6 and W12 in the placebo group but decreased in the balenine-treated group. This was particularly evident at W6, where a statistically significant decrease in the BAP ratio in the balenine-treated, group was observed compared to the placebo group (Figure 6). This result suggests that balenine intake altered the antioxidative and stress states of subjects in this study. The glucocorticoid cortisol is an adrenocortical hormone whose physiological levels in the saliva are known to increase in response to stress [17]. Salivary cortisol levels at W6 and W12 were measured and expressed as a ratio to W0 levels. In both the balenine- and placebo-treated groups, a decrease in the mean levels of cortisol was observed at W6 and W12 compared to baseline (i.e., less than 1), but the differences were not statistically significant despite a strong trend seen for the balenine-treated group at W6 (Figure 7). These results suggest that ingesting balenine over an extended period of time may be associated with anti-stress effects.

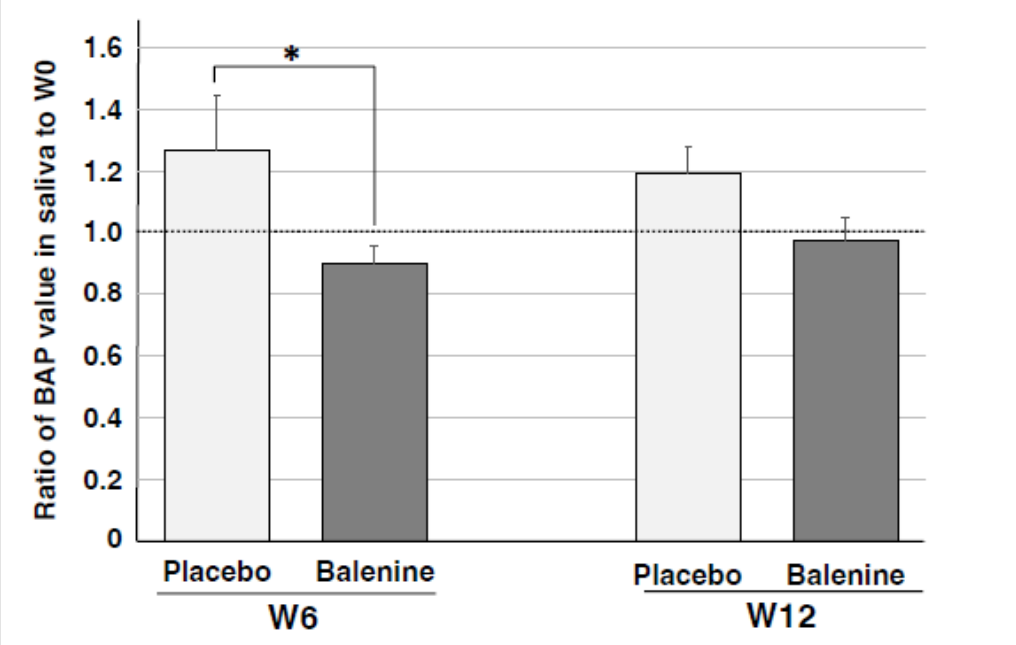

Figure 6: Effect of balenine intake on antioxidant substance levels in saliva.

Note: Ratio of BAP value in saliva at 6 weeks (W6) and 12 weeks (W12) versus baseline levels (W0). Values are expressed as the mean + SEM. *$p < 0.05$.

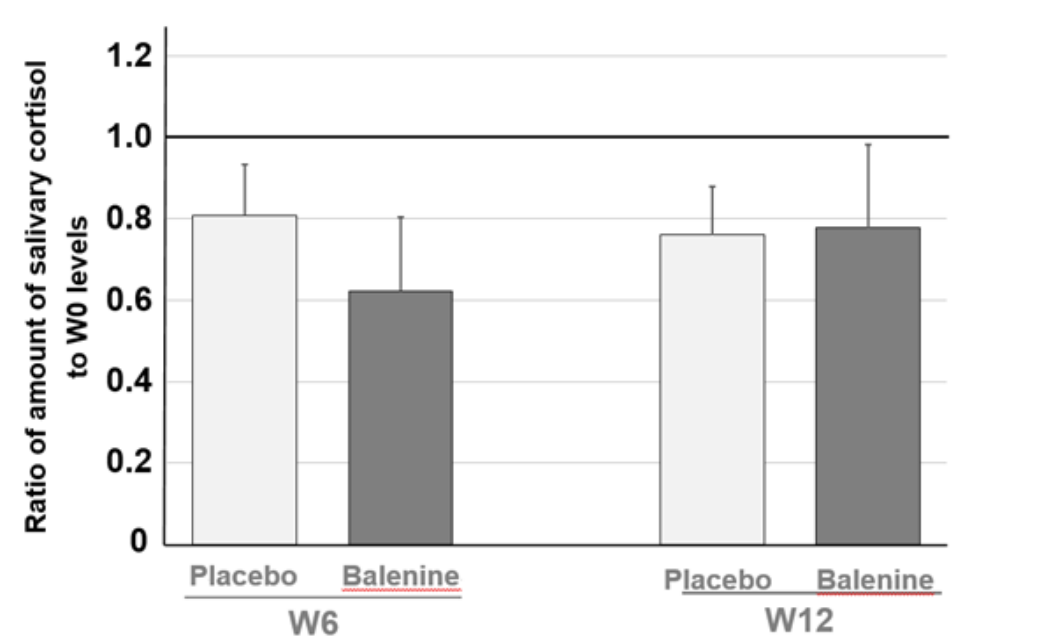

Figure 7: Effect of balenine intake for psychological stress.

Note: Ratio of salivary cortisol levels at 6 weeks (W6) and 12 weeks (W12) versus baseline levels (W0). Values are expressed as the mean + SEM.

Discussion

Previous studies by us on a mouse model of dementia (SAMP8) revealed that long- term continuous administration of balenine improves short- and long-term memory in this model [6]. Based on those results, we aimed to evaluate whether older people with symptoms of dementia might also benefit from the consumption of balenine contained in whale meat extracts. To this end, men and women aged 60 to 79 and who felt that their forgetfulness had increased as a subjective symptom were recruited to the study. Although improved cognitive function (MMSE) was observed in both the balenine- treated and placebo groups in this study, no difference was observed between the two groups (Figure 2). Similarly, the results of MCI screening were also improved in both groups, however, there was no significant difference between the two groups (Figure 3). These results suggest that the act of ingesting the capsules or participating in this study itself may have been effective for improving cognitive function. On the other hand, although there were no differences in MCI screening scores between the two groups analysis by gender showed improvement in male subjects (Figure 3). Further study is nevertheless needed given the small number of subjects in this study. As for the MMSE, the Zung SDS analysis also highlighted non-statistically significant improvements in both groups, in this case in relation to depression (Figure 4). This again suggests that ingesting the capsules or participating in the study were effective for improving the depressive state of subjects. A correlation between cognitive impairment and depression has been reported, wherein it was shown that most patients with dementia also suffer from depression [18-20]. From the above, it could be postulated that balenine may improve the depressive state observed in many patients with dementia. Since stress is critically involved in the development and progression of dementia [21], we also examined salivary BAP and cortisol levels as indicators of stress in subjects in this study (Figures 6 & 7). Our findings indicated that stress was reduced both in the balenine- and placebo-treated groups, though overall outcomes generally favored the balenine- treated group. Fatigue is a major cause of stress, and previous studies have shown that whale meat and chicken meat containing an imidazole dipeptide such as balenine have anti-fatigue effects [7,22]. These results suggest that the whale meat extract containing a large amount of balenine could reduce the progression of dementia by reducing fatigue- induced stress.

Finally, the number of answers in Uchida-Kraepelin test was significantly increased in the balenine-treated group as compared to the placebo group after 12 weeks (Figure 5), which suggests that balenine may improve cognitive function, work efficiency and concentration. Although we did not address the mechanism of action of balenine in the present study, gene expression analysis by DNA microarray in our previous studies on SAMP8 mice suggested that balenine may positively affect glucose levels and gluconeogenesis, as well as ethanol fermentation, fatty acid degradation, aromatic amino acids, and the tricarboxylic acid cycle [6]. In addition, it has been reported that treatment of a transgenic mouse model of Alzheimer's disease (AβPPswe/PSEN1dE9) with the imidazole dipeptide anserin

for 8 weeks resulted in recovery of memory deficits by providing a protective effect on the neurovascular network, which is composed of endothelial cells, pericytes, and supporting glial cells [23]. These results suggest that balenine may also exert its action via protective effects on the neurovascular system in a manner similar to that of anserine. From the above results, it is possible that the long-term ingestion of whale meat extract containing balenine may improve dementia-related deficits by reducing psychological stress. Furthermore, it is suggested that balenine may provide additional effects such as reduced depression, improvement in work efficiency, and increased concentration. Larger-scale clinical trials will be necessary to clarify these initial observations.

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Disclosure Statement

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