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Impact of Moringa Seed Extract on Daily Fatigue and Low Back Pain:

A Randomized, Parallel, Double-Blind, and Placebo-Controlled Study

Kazuo SHIMIZU／Aya ABE*／Mahendra P. KAPOOR／Zenta YASUKAWA／Makoto OZEKI

Nutrition Division, Taiyo Kagaku Co., Ltd.
1-3 Takaramachi, Yokkaichi, Mie 510-0844, Japan.

● **Abstract**

Objective: The objective of this study was to examine the effect of moringa seed extract containing glucomoringin (GMG) on fatigue in healthy working men and women.
Methods: Healthy adult working men and women (forty participants, Male: 18; Female: 22) were enrolled in this randomized, parallel, double-blind, and placebo-controlled study. The participants took 120 mg of moringa seed extract (GMG; 12 mg) or placebo every day for four consecutive weeks. The severity of fatigue and physical discomfort were evaluated with a Visual Analog Scale (VAS) and Chalder fatigue scale at baseline and every week of the study duration. A medical interview with a study physician was conducted at the baseline and end of the study.
Results: Intake of moringa seed extract led to the significant decrease in VAS scores of fatigue, low back pain, stiff shoulder, and eye strain. A difference in low back pain VAS scores from baseline was significantly higher in the treatment group than the placebo group after two weeks. Among the subjects with higher fatigue VAS score subgroups, the change was considerably more significant after four weeks in the treatment group. In the higher low back pain VAS score subgroups, the difference from the baseline scores was considerably more significant after 2, 3, and 4 weeks among the subjects of treatment group.
Conclusion: The consumption of moringa seed extract is found effective in lowering the severity of fatigue and low back pain among the healthy working men and women of middle age subjects with somewhat severe symptoms.

Key words: Moringa, Moringin, Glucomoringin, Fatigue, Low back pain

1. *Introduction*

Fatigue is a symptom caused by physical and psychological stress, and it is a severe problem in modern society that affects human health, work efficiency, and quality of life. In recent years, technological innovations such as information communication have advanced, and changes in working conditions have increased the opportunities for using computer devices, and that resulted in the increased physical and mental fatigue. According to a survey conducted in 2003 by Japan's Ministry of Health, Labor and Welfare on 14,000 office workers in Japan's privately-owned business offices and sales divisions; 86.2% of workers were using computer and 78% of workers felt physical fatigue and related symptoms, and many workers felt eye strain (91.6%), stiff shoulder (70.4%), and low back pain (26.6%)[1]. Thus, the problem of fatigue has become a serious problem not only in the working people, but also in the whole society, and the effective solution is needed. Since there are not enough pharmacological supplies for fatigue recovery, therefore, non-pharmacological approaches such as functional foods are currently promising, and likely to become of an increasing importance.

Moringa oleifera (Moringaceae) is a perennial tree native to the northwestern part of India and is now widely distributed in tropical areas. It is highly nutritive, and young fruits and leaves are mainly eaten as vegetables, and leaves are utilized as supplements, besides, to use as a tea, and fruits containing seeds are locally used as curry ingredients[2)3)]. Not only as a food, but moringa is also said to have 300 medicinal effects in folk medicine "Ayurveda", and has been widely used since BC[4)~6)]. Recently, numerous pharmacological effects of moringa has been shown *in vivo* and *in vitro* including antibacterial, digestive aid, appetite suppression, anti-inflammatory, immune improvement, cholesterol reduction, blood pressure control, visual improvement, antidepression, cognitive function improvement, anti-fatigue, and so on[7)~14)]. *Moringa oleifera* is a rich source of β-carotene, protein, vitamin C, calcium and potassium

* Corresponding author; E-mail address:aabe@taiyokagaku.co.jp (A.Abe)

and act as a good source of natural antioxidants. It also contains unique bioactive compounds represented by glucosinolates primarily glucomoringin (GMG; 4 (α -L-rhamnosyloxy)-benzyl glucosinolate)[12]. GMG undergo enzymatic conversion to moringin, one type of isothiocyanates by host gut microbiota [15]. To date, moringin has been shown to have numerous pharmacological effects including as chemoprotective agent against cancer progression and direct antitumoural effects along with antioxidant and anti-inflammatory properties both *in vivo* and *in vitro* [7)16)~19)]. Anti-fatigue effect of moringa leaves extract has already shown in rats subjected to forced swimming endurance test [20], and we confirmed the same effects of moringa seed extract in our previous study [21]. Wherein, intake of feed containing GMG at 0.2 mg/kg/day for four weeks was found to improve fatigue during forced swimming. In this study, we investigated the anti-fatigue effect of moringa seed extract in a clinical trial. We designed a randomized, parallel, double-blind, and placebo-controlled study to investigate the anti-fatigue effect of moringa seed extract.

2. *Materials and Methods*

2.1. Ethical approval of the study protocol

The study was conducted in accordance with the Helsinki Declaration based on the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (Notification by the Ministry of Health, Labor and Welfare, partially revised on February 28, 2017). The institutional review board approved the study protocol at Ueno-Asagao Clinic (Approval number: 2019-09; Date of approval: January 24, 2019). The study protocol was registered at the UMIN-CTR (Trial ID: UMIN 000035949). The protocol was not modified from the time of final setup and during the study.

2.2. Supplementation and dosages

Tablets of moringa seed extract containing GMG (Taiyo Kagaku Co., Ltd., Japan) were prepared as treatment food. Based on our previous study [21], the effective dosage for human was estimated, and 12 mg of GMG/day was chosen for this study. Tablets without moringa seed extract, but containing dextrin as a substitute were used as placebo. Composition of a single dose of treatment (moringa seed extract) and placebo are shown in **Table 1**. There was no difference in appearance or flavor between the treatment and placebo tablets. Concerning to the safety, a single-dose toxicity test (maximum dose 5,000 mg/kg), 90-days repeated dose toxicity test (maximum dose 1,000 mg/kg/day), and teratogenicity test (maximum dose 1,473 mg/kg/day) of studied moringa seed extract showed no adverse effects. Further, a preliminary in-house test with 120 mg of moringa seed extract (GMG; 12 mg) /day for two weeks also showed no adverse effects (unpublished in-house data).

Table 1　Composition of single dose of treatment（Moringa seed extract; MSE）and placebo（PLA）※.

Description		Moringa seed extract	Placebo
Energy	(kcal)	1.949	1.956
Protein	(g)	0.010	0.001
Fat	(g)	0.013	0.013
Carbohydrate	(g)	0.966	0.978
Sodium	(mg)	0.132	0.034
Moringa seed extract	(mg)	120	0
└ Glucomoringin	(mg)	12	0

※Seven（7）tablets / day.
［MSE: 120 mg: 3 tablets（40 mg/ tablet）+ placebo 4 tablets］
［PLA: placebo 7 tablets］

2.3. Participants

Healthy adult working men and women, aged 30-64 years were recruited as paid volunteers. All participants received explanatory documents and consent forms. The purpose and the protocol procedures of the study were thoroughly explained. Finally, the 112 subjects who expressed consent were enrolled for the study.

As a preliminary examination, the subjects' lifestyle habit questionnaires, blood pressure, heart rate, height, weight, body fat, body mass index (BMI) were investigated. The severity of fatigue and physical discomfort (low back pain, stiff shoulder, and eye strain) was rated on Visual Analog Scale (VAS)[22]. Chalder fatigue scale (Japanese version)[23] and Profile of Mood States Short form 2 (POMS-2, Japanese version)[24] were also scored.

Inclusion criteria were (1) Japanese males and females aged 30-64 years; (2) subjects who are healthy and are not received treatment of disease; (3) subjects who have daily fatigue; (4) subjects who have stiff shoulder, low back pain, or eye strain derived from fatigue; (5) subjects who work on daytime from Monday to Friday and have Saturdays and Sundays off; (6) subjects whose written informed consent has been obtained; (7) subjects who can come to the designated venue for this study and be inspected. (8) subjects judged appropriate for the study by the principal investigator (Takahiro Ono, Ueno-Asagao Clinic). Exclusion criteria were (1) subjects who have chronic fatigue; (2) subjects using medical products; (3) subjects who are patient or have a history of psychiatric disease, high blood pressure, diabetes, and hyperlipidemia; (4) subjects who used a drug to treat a disease in the past 1 month (except temporal usage for hay fever); (5) subjects who have a history of acute liver dysfunction, kidney damage, heart disease and hematological disease; (6) subjects who are a patient or have a history of or endocrine disease; (7) subjects whose

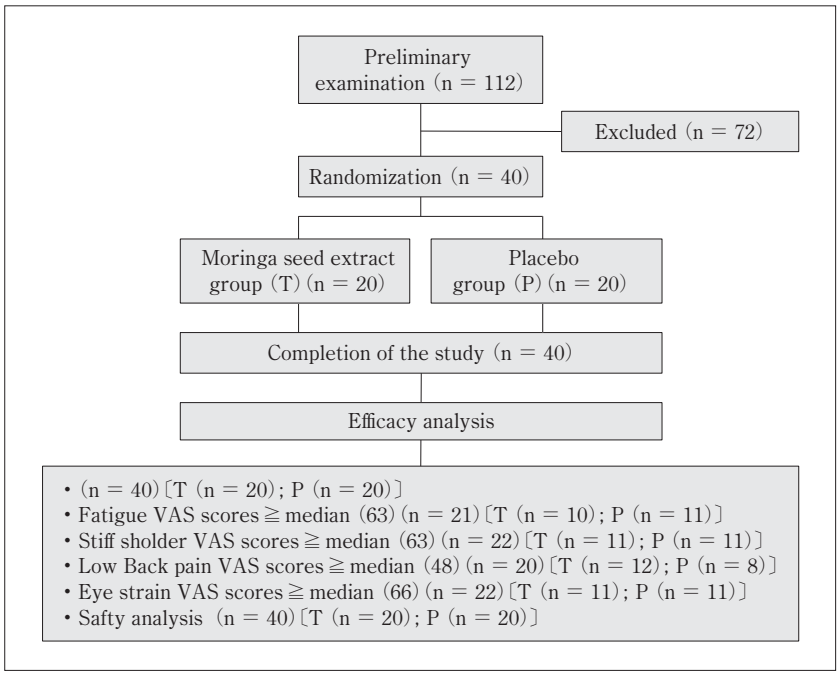

Figure 1 Systematic flow chart of the study

BMI is over 30; (8) subjects with severe anemia; (9) subjects who are sensitive to a test product or other foods, and medical products; (10) subjects who excessively take alcohol (expressed in an amount of alcohol: over 60 mg/day); (11) subjects with possible changes of life style, such as conducting a long-term travel, during the test period; (12) subjects who had a habit to ingest health-promoting foods, foods for specified health uses, health foods, or supplements with components contained in the test product in the past three months or will ingest those foods during the test period; (13) subjects who are or are possibly pregnant, or are lactating; (14) subjects who participated in other clinical studies in the past three months; (15) subjects who are or whose family is engaged in functional foods or cosmetics company; (16) subjects judged inappropriate for the study by the principal investigator.

2.4. Sample size

Based on the previous study that evaluated the effects of broccoli-derived glucosinolates, structural analogs of GMG on liver functions[25], we decided to recruit forty participants (twenty in each intervention group) for this study, which is theoretically necessary to detect a difference (changes from baseline). The candidates were first screened according to the inclusion/exclusion criteria, and then forty (n = 40) subjects were recruited in the order of total scores of VAS fatigue scores, Chalder fatigue scale scores, and "fatigue-inertia" scores of POMS-2.

2.5. Study design

The study was performed in a randomized, parallel, double-blind, and placebo-controlled manner, and a systematical flow chart of study protocol is illustrated in **Figure 1**. The forty (n = 40, M: 18; F: 22) participants were randomly assigned to the moringa seed extract or placebo supplementation groups using a stratified block randomization design stratified by age, fatigue VAS scores, Chalder fatigue scale scores, and "fatigue-inertia" scores of POMS-2. The allocation of subjects was performed by TES Holdings Co., Ltd. (Tokyo, Japan), and the concerning information was concealed from both the subjects as well as the investigators until the completion of the intervention study.

2.6. Schedule

The study was carried out at Ueno-Asagao Clinic (Taito-ku, Tokyo) from February to March 2019. The participants took seven tablets every day after breakfast for four weeks (see **Table 1**). During the study period, subjects were instructed to maintain their usual lifestyle and refrain from taking pharmaceuticals (including external preparation), quasi-drugs, Chinese medicine, and functional food, and in case of taking any of the above, they were required to log in their daily log book. Subjects were instructed to refrain from the excessive exercise and alcohol consumption from the day before the clinic visit. The subjects were also instructed to log details in the log book, including their tablets ingestion, physical condition, use of pharmaceuticals, and any adverse events.

During the study period of 1 to 3 weeks, the subjects rated the severity of fatigue and physical discomfort on VAS and Chalder fatigue scale at home every week after the respective intervention. After four weeks, the

Table 2　Baseline characteristics of forty（n＝40）subjects selected through preliminary examination.

		Treatment group (n = 20)	Placebo group (n = 20)
Gender	(Male/Female)	9 / 11	9 / 11
Age	(years)	49.3 ± 3.5	48.9 ± 7.8
Weight	(kg)	62.5 ± 12.6	57.4 ± 9.5
Body fat	(%)	26.6 ± 6.6	24.4 ± 4.7
Body Mass Index	(kg/m^2)	22.6 ± 2.5	21.5 ± 2.0
Systolic blood pressure	(mmHg)	116.0 ± 12.9	116.7 ± 12.5
Diastolic blood pressure	(mmHg)	71.8 ± 9.5	74.0 ± 9.0
Heart rate	(bpm)	70.7 ± 9.1	72.0 ± 13.2
Fatigue VAS scores	(mm)	63.1 ± 15.3	60.6 ± 11.9

Values represented as Mean ± SD.

subjects again visited the clinic and severity of fatigue (VAS, Chalder fatigue scale, POMS-2 questionnaires), blood pressure, heart rate, weight, body fat, BMI was investigated, and a medical interview with study physician was conducted.

The primary outcome was a subjective evaluation of fatigue (rated with VAS, Chalder fatigue scale, POMS-2 questionnaires), and as the secondary outcome, the safety of moringa seed extract was evaluated with blood pressure, heart rate, weight, BMI, medical interview and daily log book.

2.7. Methods of evaluation of fatigue

Visual Analog Scale (VAS): The subjects were instructed to rate their fatigue level or physical discomfort level on VAS from 0 (no fatigue) to 100 (extreme fatigue).

Chalder fatigue scale: A four-step questionnaire which contains 14 questions about the level of fatigue.

Profile of Mood States Short form 2 (POMS-2): A five-step questionnaire which contains 65 questions that describe seven different moods as follows: "anger-hostility", "confusion-bewilderment", "depression-dejection", "fatigue-inertia", "tension–anxiety", "vigor-activity" and "friendliness".

2.8. Statistical analysis

Values are presented as means ± standard deviations. As a parametric test, we used the paired *t*-test for intragroup comparison and the Student's *t*-test for intergroup comparison. As the non-parametric test, the Wilcoxon signed rank-test for intragroup comparison and the Mann-Whitney *U*-test for intergroup comparison were employed. Additionally, to clarify the effects of moringa seed extract on the subjects with more severe symptoms, we divided the subjects into subgroups with respect to the median of each baseline VAS scores, and analyzed the groups with abobe median baseline scores: higher fatigue VAS scores subgroups, higher stiff shoulder VAS scores subgroups, higher low back pain VAS scores subgroups, and higher eye strain VAS scores subgroups. Statistical analyses were performed using SAS (SAS 9.4) or SPSS (Statistics 25) and p-value of < 0.05 was considered to be significant.

3. *Results*

3.1. The baseline characteristics of participants

The subjects were recruited from January 25, 2019 to February 7, 2019. Of the forty subjects who participated in this study, all subjects completed this trial, and no subject was excluded from the analysis following the set protocol (**Figure 1**). **Table 2** lists the baseline characteristics of forty subjects selected thorough a preliminary examination (gender, age, weight, body fat, BMI, systolic blood pressure, diastolic blood pressure, heart rate, fatigue VAS scores). There was no significant difference in any of the variables between the moringa seed extract supplementation group and the placebo group.

3.2. Efficacy evaluation

Table 3 displays the VAS scores of fatigue, stiff shoulder, low back pain, and eye strain before the intake of moringa seed extract treatment, and changes from the baseline at 1, 2, 3, and 4 weeks after the supplementation. Intake of moringa seed extract tablets led to the significantly decreased respective VAS scores, whereas a certain level of effectiveness could also observed in the placebo group. However, a significant difference between the groups for the estimated change in low back pain VAS scores from baseline could be observed after 2 weeks; with the moringa seed extract group showing a marked decrease value (treatment: − 13.8 ± 23.2, placebo: 3.1 ± 16.4). Also, the intervention of the treatment and the placebo tablets led to the significantly decreased many categories of scores of Chalder fatigue scale and POMS-2, but there was no significant difference between groups (data, not shown).

Table 3 VAS scores of fatigue and other physical discomfort parameters (n = 40)

Category	Group	Baseline Scores	(Median)	Changes from the baseline			
				Week 1	Week 2	Week 3	Week 4
Fatigue	T (n = 20)	63.1 ± 15.3	(63)	− 18.8 ± 21.1	− 25.2 ± 18.4	− 28.0 ± 19.4	− 27.6 ± 22.5
	P (n = 20)	60.6 ± 11.9		− 10.2 ± 17.5	− 14.4 ± 17.3	− 16.6 ± 20.9	− 17.4 ± 19.5
Stiff shoulder	T (n = 20)	61.7 ± 18.8	(63)	− 15.3 ± 21.0	− 19.7 ± 19.6	− 24.4 ± 21.2	− 25.5 ± 22.8
	P (n = 20)	61.7 ± 17.4		− 15.7 ± 15.1	− 14.4 ± 15.8	− 17.0 ± 20.4	− 22.7 ± 17.6
Low back pain	T (n = 20)	49.1 ± 24.5	(48)	− 9.5 ± 21.6	− 13.8 ± 23.2*	− 18.3 ± 28.7	− 17.5 ± 32.3
	P (n = 20)	36.7 ± 24.5		− 2.1 ± 12.4	3.1 ± 16.4	− 4.0 ± 16.5	− 8.3 ± 15.0
Eye strain	T (n = 20)	65.8 ± 17.1	(66)	− 9.6 ± 16.5	− 19.3 ± 20.8	− 19.4 ± 25.4	− 28.2 ± 17.4
	P (n = 20)	67.4 ± 11.1		− 18.9 ± 20.1	− 16.6 ± 19.7	− 20.2 ± 21.6	− 25.8 ± 21.7

Values represented as Mean ± SD.
T = Moringa seed extract (Treatment); P = Placebo
*$p < 0.05$ between groups

Table 4 Analysis of VAS scores of the subjects with above median baseline scores※.

Category	Group	Baseline Scores	Changes from the baseline			
			Week 1	Week 2	Week 3	Week 4
Fatigue	T (n = 10)	74.9 ± 8.1	− 31.5 ± 16.3	− 33.2 ± 17.3	− 36.6 ± 18.1	− 43.4 ± 15.8*
	P (n = 11)	68.8 ± 6.0	− 15.8 ± 20.5	− 16.6 ± 20.3	− 19.9 ± 24.6	− 18.7 ± 24.6
Stiff shoulder	T (n = 11)	75.3 ± 8.5	− 19.8 ± 22.3	− 24.7 ± 22.8	− 31.1 ± 24.9	− 36.5 ± 23.9
	P (n = 11)	73.3 ± 9.4	− 17.0 ± 12.7	− 18.8 ± 11.9	− 26.0 ± 14.1	− 27.8 ± 15.7
Low back pain	T (n = 12)	65.9 ± 12.2	− 16.4 ± 19.4	− 23.1 ± 17.6**	− 32.4 ± 21.1*	− 34.8 ± 19.5*
	P (n = 8)	60.3 ± 10.9	− 7.6 ± 8.5	− 6.0 ± 7.0	− 10.4 ± 12.0	− 12.4 ± 14.8
Eye strain	T (n = 11)	77.7 ± 8.1	− 12.3 ± 12.9	− 25.2 ± 16.3	− 27.8 ± 20.5	− 30.2 ± 18.0
	P (n = 11)	74.3 ± 9.8	− 26.8 ± 19.9	− 20.7 ± 19.8	− 19.9 ± 22.9	− 31.2 ± 20.8

Values represented as Mean ± SD.
T = Moringa seed extract (Treatment); P = Placebo
※Baseline median values: Fatigue (63), Stiff shoulder (63), Low back pain (48), Eye strain (66)
*$p < 0.05$, **$p < 0.01$ between groups

To clarify the effects of moringa seed extract on subjects with somewhat severe symptoms, we divided the subjects into subgroups considering the median of each baseline VAS scores and analyzed subjects with abobe median baseline scores. **Table 4** shows the VAS scores of the subjects with above median baseline scores. In the higher fatigue VAS score subgroups, there was a significant difference between the groups in respect to change from the baseline after 4 weeks; with the treatment group showing a marked decrease value (treatment: − 43.4 ± 15.8, placebo: − 18.7 ± 24.6) (**Figure 2**). Whereas, in the higher low back pain VAS score subgroups, there were significant differences between the groups in respect to change from the baseline at week 2, 3, and 4; with the treatment group showing a marked decrease values (at week 2, treatment: − 23.1 ± 17.6, placebo: − 6.0 ± 7.0; at week 3, treatment: − 32.4 ± 21.1, placebo: − 10.4 ± 12.0; at week 4, treatment: − 34.8 ± 19.5, placebo: − 12.4 ± 14.8) (**Figure 3**). Therefore, it can be postulated that the supplementation of moringa seed extract mitigated the severity of fatigue and low back pain among the subjects with somewhat severe symptoms.

3.3. Safety

There was no report of any adverse event resulting from the intake of the treatment tablets. Some relative changes in body weight, BMI, heart rate were observed in the moringa seed extract treatment group. However, these were within normal limits of daily variation and were not considered to be due to moringa seed extract by the principal investigator.

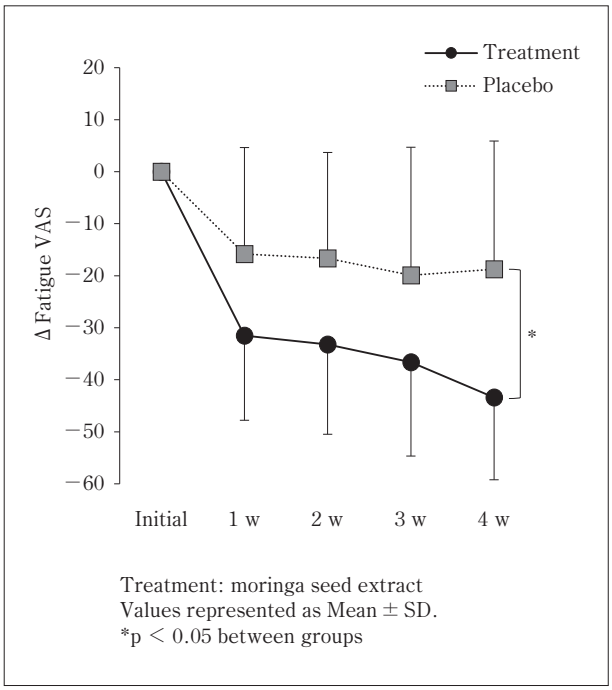

Figure 2　Changes in fatigue VAS scores of the subjects with abobe median baseline scores during the study period.

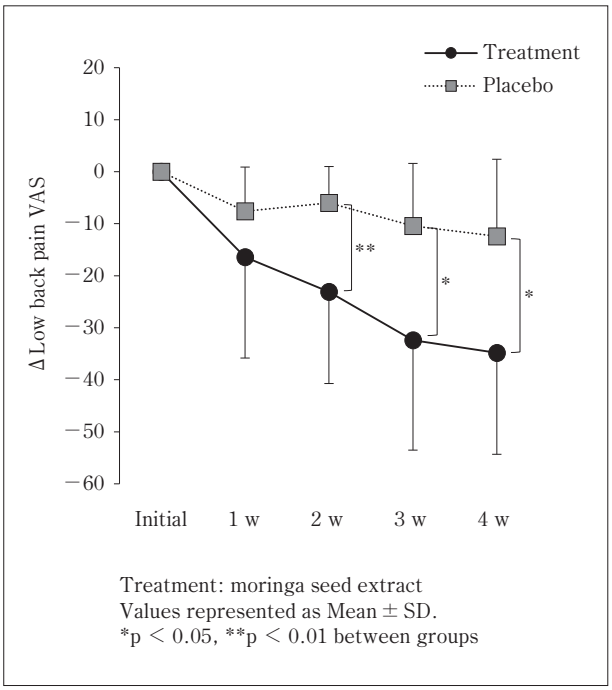

Figure 3　Changes in low back pain VAS scores of the subjects with abobe median baseline scores during the study period.

4. *Discussion*

In the present study, we evaluated the effect of moringa seed extract on daily fatigue in a randomized, parallel, double-blind, and placebo-controlled study. The results indicated that moringa seed extract mitigated fatigue and low back pain in the subjects whose symptoms were somewhat severe in the treatment group compared to the placebo group. It has been demonstrated that oxidative stress is one of the main factors leading to fatigue [26]. In the human body, the reactive oxygen species (ROS) are generated and in normal condition usually disappears rapidly. However, when cellular overproduction of ROS overwhelms intrinsic antioxidant capacity, the oxidative stress occurs, and the damage to the biomolecules of normal cells and tissues might occur [27]. ROS increases oxidized proteins, and lipid peroxides inhibit normal cell function and cause inflammation, which causes increased fatigue and physical discomfort [28][29]. This suggests that supplementation of antioxidants that capable to reduce ROS could potentially contribute to fatigue recovery.

Moringa seed extract used in this study contains GMG, which is considered to be converted to moringin by host gut microbiota. In the previous study, moringin has been shown to mitigate the increase of intracellular oxidative stress induced by H_2O_2 on retinoic acid-induced differentiated neuroblastoma cells [17]. Moringin pre-treated neuron cells showed significant resistance to H_2O_2 -induced apoptotic cell death, revealing a high level of antioxidative effect [17]. Moringin was also shown to increase antioxidant Nrf2 expression, suppress the primary inflammatory mediators, and regulate T-cell activation in a mouse model of experimental autoimmune encephalomyelitis [30]. Moringin was also reported to modulate not only the inflammatory pathway, but also oxidative stress and apoptotic pathways in a mouse model of subacute of Parkinson's disease [18]. Related findings suggest the antioxidant and anti-inflammatory effects of moringin could be considered as a postulated mechanism of the anti-fatigue effect of moringa. Anti-fatigue characteristics of moringa leaves extract have already demonstrated in rats subjected to a forced swimming endurance test, along with enhancing the activity of antioxidant enzymes, and lowering the blood concentration of malondialdehyde, a significant marker of oxidative stress [20]. Additionally, in our previous *in vitro* study with cell culture, wherein GMG extracted from moringa seeds was further converted by the enzyme into moringin, and showed activation of PPAR β/δ [21]. Activation of PPAR β/δ has been reported to be involved in the improvement of muscle endurance [31]~[33], and might be considered as another mechanism of the anti-fatigue effect of moringa. In reference to the above reports, the fatigue and low back pain improvement effects of moringa seed extract of this human clinical study are likely due to the combined effects of antioxidant, anti-inflammatory, and activation PPAR β/δ activities of GMG contained in moringa seed extract. Therefore, GMG is suggested to be a primary component involved in lowering the severity

of fatigue, and low back pain originated from antioxidant activity.

Noteworthy to mention that a certain level of effectiveness could be observed in the placebo group of this study, which could be attributed to fatigue feelings that were influenced by respective environmental and physiological parameters. This could be a one of the possible reason that the impact of moringa seed extract was not appropriately evaluated due to the above mentioned positive influence of placebo. Since the present study targeted at healthy subjects who feel temporary fatigue, it might be difficult to assess the desired effect. However, among the subjects with somewhat severe fatigue symptoms, the placebo intake did not influence fatigue and low back pain alleviating effects over time, whereas moringa seed extract intake showed a considerable impact. The finding supports the effectiveness of moringa seed extract on fatigue and low back pain.

Concerning the safety, no adverse events or any side effects could be noticed during the moringa seed extract intervention period. Thus, considering the safety viewpoint, the consumption of 120 mg of moringa seed extract (GMG; 12 mg) /day for four consecutive weeks is found very safe.

5. *Conclusion*

The results of the present study demonstrated that intervention of moringa seed extract was found effective in lowering the severity of fatigue as well as low back pain in the subjects whose symptoms were somewhat severe among the healthy working men and women of middle age. However, further comprehensive studies are needed to design with a large sample size and diversity of the population to evaluate the potential of moringa seed extract and related products.

【*Conflict of interest statement*】

Taiyo Kagaku Co., Ltd. provided the funding for this study, and there are no other conflicts of financial interests to declare.

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