ORIGINAL ARTICLE

Clinical Effect of Oral Administration of Maca (Lepidium meyenii) Extract on Japanese Peri-Menopausal Women Subjects: A Randomized, Double-Blind, Placebo-Controlled Study

Tsuyoshi Takewaka[1], Kiyoshi Hara[2]

[1]Comedical Laboratory Co., Ltd., 1-1-5-1203, Zengyohzaka, Fujisawa-shi, Kanagawa 251-0876, Japan;
[2]Latina Inc., 4-25-7, Kamata, Ohta-ku, Tokyo, Japan

ABSTRACT

Background: Roots of *Lepidium meyenii* (Maca) is traditionally used as a food supplement for its rich nutritional property in Andes of Peru for thousands of years. Native Peruvian have further expanded Maca usage in medicine to enhance fertility and aphrodisiac in both human and live stocks and to treat menopausal disorders.

Objective: We examined the effect of Maca extract containing at least 1.2% of benzylglucosinolate (Maca-BG1.2™) on the serum level of hormones and menopausal disorder of Japanese peri-menopausal women.

Methods: a randomized, double-blind, placebo controlled, parallel clinical study was carried out in a period of 8 weeks, levels of estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH) and progesterone (PGS) in sera of baseline (week 0) and week 8 were compared. As for menopausal disorder, we compared the simplified menopausal index (SMI) of all the cohorts. 42 healthy peri-menopausal Japanese women (aged 40 to 58 years) were randomly allocated to two groups, one receiving Maca-BG1.2™ for 8 weeks and the other receiving placebo. All participants signed informed consent forms. Two hard gel capsules with 150 mg Maca-BG1.2™ or 180 mg placebo were self-administered by participants once daily after breakfast.

Results: after 8 weeks administration of Maca-BG1.2™, the E2 level was significantly increased in the sera of peri-menopausal women with periodical menstruation. insomnia, one key SMI, was also elevated and mild menopausal disorder peri-in menopausal women was alleviated by Maca-BG1.2™.

Conclusion: These results showed that Maca-BG1.2™ may be a useful non-hormonal plant material for Japanese peri-menopausal women. (*Int J Biomed Sci* 2019; 15 (1): 11-18)

Keywords: Maca; estradiol (E2); insomnia; peri-menopausal women

Corresponding author: Tsuyoshi Takewaka, 1-1-5-1203, Zengyohzaka, Fujisawa-shi, Kanagawa 251-0876, Japan. TEL: + (81) 3 3738 5017; FAX: + (81) 3 3738 5020; E-mail: takewaka1972@gmail.com.
Received November 6, 2018**; Accepted** March 1, 2019

INTRODUCTION

Hormone replacement therapy (HRT) is traditionally used to treat woman menopausal disorders (1). Due to HRT's adverse effects, more women have seeked alternative treatment options. a recent study revealed that over 40 % of Japanese women had used complementary and alternative medicines or therapies to alleviate menopausal disorders (2) and around 70 % would like to choose complementary and alternative medicine in the future for menopausal disorders (3).

Maca (*Lepidium meyenii*) is an herbaceous plant belonging to the Brassicaceae family, and it has been cultivated at the Peruvian central Andes (above 4,000 m a.s.l) since the times of Incas. In Peru, the harvested roots (also called as hypocotyl) of Maca is dried in the open air for about 3 months before used. About 60 to 250 g of the dried Maca is typically consumed daily by a Peruvian person for cooking, making sweets or drinks (4). Maca is a nutritional rich food supplement that contains hydrocarbon, protein, fatty acid, minerals and many kinds of phytochemicals. In addition, Maca has also been used for medicinal supplement to enhance fertility and aphrodisiac as well as relieve menopausal disorders for long time (5-13). A clinical trial of Maca on menopausal symptoms in Caucasians demonstrated that Maca may be a good alternative of HRT (12, 13). Nevertheless, another study showed that Maca only displayed a limited effect on menopausal disorders of the Mongolian Hong Kong Chinese (14), raising a question whether Maca's effect on menopausal disorders is race-dependent. Furthermore, the mechanism by which Maca may affect menopausal symptoms remained to be elucidated.

The aim of this study was to examine the effect of oral administration of Maca extract on serum hormone levels and menopausal symptoms in peri-menopausal Japanese women. In a randomized, double-blind, placebo controlled, parallel trial, changes in serum sex hormone levels were examined in 41 peri-menopausal women. Menopausal disorders were examined using SMI, modified questionnaires to Japanese. To our knowledge, this is the first study examining the effects of Maca in Japanese women.

MATERIALS AND METHODS

Plant material

The washed, sliced and oven dried Maca cultivated in high plateaus of Andes was purchased from CPX PERU S.A.C. (Lima, Peru), and they were subjected to extract by hydrous ethanol and evaporation to prepare powdered named Maca-BG1.2™ containing at least 1.2% benzylglucosinolate.

Subjects

ORTHO MEDICO (Tokyo, Japan), a CRO company, helped recruit 42 Japanese subjects, aged between 40 to 59 years for this study. They were peri-menopausal women in good overall healthy conditions and with relatively high level of follicle stimulating hormone. Subjects were never on HRT, had no history of any cancer, cardiovascular disease, cerebrovascular disease, liver disease, kidney disease, rheumatism, diabetes, dyslipidemia, hypertension, and allergy to dietary supplement ingredients or medicine ingredients. Subjects were required not to consume any supplements during the study.

Study design

The study protocol was approved by the Clinical Research Ethics Committee of the Takara Clinic and written consent forms were obtained from all participants. This was an 8-week, randomized, single center, double-blind, placebo controlled, parallel trial. 41 out of 42 women completed the trial. 21 women received 2 × 150 mg Maca-BG1.2™ capsules daily and 20 women received 2 × 180 mg dextrin capsules daily. Appearance of each capsule were identical. Capsules were self-administered after the morning meal for the period of 8 weeks.

Participant's compliance with treatment was monitored

At baseline and week 8, venous blood and urine samples were collected. Blood samples were for the measurement of serum estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone (PGS), hematological examination and blood biochemistry. Urine samples were for urine test. At baseline and week 8, women also completed the SMI and Likert type adverse effect questionnaires (AEQ). The cohorts were interviewed to determine SMI for any change in the severity of their menopausal disorders, and examine AEQ for the safety of receiving Maca-BG1.2™. Participants' heights, bodies, weights, Body Mass Indexes, blood pressures and heart rates were also taken.

Measurement

Serum E2, FSH, LH and PGS were analyzed using the Abbott ARCHITECT i2000 with CLIA technology (Abbott Japan, Tokyo, Japan). Urine test was analyzed using the EIKEN US-3100R with Uropaper alphaIII Eiken

(Eiken, Tokyo, Japan). Hematological examination was analyzed using Sysmex XE-2100 (Sysmex, Hyogo, Japan). Blood biochemistry was analyzed with a calorimetric test using H7700 (Hitachi high technologies, Tokyo, Japan). kits to measure AST, ALT, gamma-GTP, ALP, LDH, LAP, total bilirubin, direct bilirubin, indirect bilirubin, total protein, urine nitrogen, creatinine, uric acid, creatine kinase, total cholesterol and triglyceride were purchased from LSI medience (Tokyo, Japan).The kit to measure choline esterase was purchased from Serotec (Hokkaido, Japan), the kit to measure ZTT was purchased from Wako pure chemical industries (Osaka, Japan), kit to measure Calcium was purchased from Nipro (Osaka, Japan), kits to measure inorganic phosphorus, HDL cholesterol and LDL cholesterol were purchased from Kyowa medex (Tokyo, Japan), kit to measure Ferrite was purchased from Shino-test (Tokyo, Japan) kit to measure amylase was purchased from Sekisui medical (Tokyo, Japan) and kit to measure free fatty acid was purchased from Eiken) or JCA-BM9130 (JOEL, Tokyo, Japan) (kit to measure glucose was purchased from LSI medience, kit to measure HbA1c was purchased from Arkray (Kyoto, Japan) and kit to measure glycoalbumin was purchased from Sekisui medical). Potassium, chlorine and sodium was analyzed with an ion-selective electrode using H7700.

Height was analyzed at ORTHO MEDICO. Body weight, body fat percentage (BFP), body mass index (BMI), blood pressure (BP) and heart rate (HR) were analyzed at Takara Clinic (Tokyo, Japan). Other analyses were done at LSI medience.

SMI is a well validated self-reported questionnaire that measures the vasomotor, physiologic and somatic symptoms associated with menopause in Japan (17). The index assesses vasomotor symptoms with subscale for hot flashes, sweats, cold constitution and shortness of breath or palpitation, physiologic symptoms with subscale for easy fatigability, shoulder stiffness and lumbago or joint pain, and somatic symptoms with subscale for insomnia, easy excitability or irritability, worry about self-depression and headache, vertigo or nausea.

Statistical analysis

Statistical analyses were performed using R (version 2.8.1). Analysis of hormone levels, hematological examination, blood biochemistry, height, body weight, body mass index, blood pressure and heart rate were performed using student's t –test if homoscedasticity or Welch's t –test if heteroscedasticity for inter-group comparisons and paired t -test for intra-group comparisons. Above data, except hematological examination, are expressed as the mean and standard error (SE). Analysis of Urine test, SMI and AEQ were performed using Mann-Whitney U -test for inter-group comparisons and Wilcoxon signed rank test for intra-group comparisons. SMI data are expressed as the median, the first quartile (FQ) and the third quartile (TQ). A p value of <0.05 was considered of statistical significance.

RESULTS

Effect of oral administration of Maca-BG1.2™ on serum hormone levels of peri-menopausal Japanese women

There was no difference between Maca group and placebo group in term of their ages and anthropometric data (Table 1). The serum E2 level, after 8weeks administration of Maca-BG1.2™, showed approximately 2.2-fold increase compared to the placebo group though it was not statistically significant (Table 2). Subjects were further classified into three groups by menstruation to analyze E2 changes to oral administration of Maca-BG1.2™, i) peri-menopause with periodical menstruation, ii) peri-menopause without periodical menstruation and iii) menopause. The data showed that the serum E2 level in the peri-menopausal subjects with regular menstruation cycle displayed a mostly significant change (about 3-time increase) between the Maca-BG1.2™group and the placebo **(**Table 3**)**. For about intra group comparison in all subjects, serum E2 level was increased in Maca group for about 1.4 times whereas decreased in placebo group for about 0.8 times (Table 2), but both were not significant.

Effect of oral administration of Maca-BG1.2™ on menopausal disorder of peri-menopausal Japanese women

The SMI previously developed by Dr. Koyama has been widely used to assess the severity of menopausal disorders (18). After 8weeks administration, score of insomnia, one index of SMI, showed a marginal decrease in the Maca group compared to the placebo group (FQ/median/TQ= 0/0/5 vs 0/5/9) (Table 4). Subjects were further divided into two groups by the total SMI score, mild menopausal disorder (total SMI score under 50) and serious (over 51). Then, we examined which subjects responded significantly to oral administration of Maca-BG1.2™. As seen in Table 5, the mild menopausal disorder subjects displayed higher response to Maca-BG1.2™ in comparison to placebo (FQ/median/TQ was 0/0/0 vs 0/4.5/9). For about intra group

comparison, score of insomnia was specifically and marginally lower in Maca group, FQ/median/TQ was 0/5/5 vs 0/0/5 whereas placebo was 0/5/9 vs 0/5/9 (Table 4), but not statistically significant.

Safety of oral administration of Maca-BG1.2™

Based on the results of urine test, blood biochemistry, hematological examination, AEQ (data not shown) and anthropometric data (Table 1), there was no serious adverse effect that we concluded that daily administration of 300 mg Maca-BG1.2™ for 8 weeks is safe.

DISCUSSION

Effect of Maca-BG1.2™ treatment in peri-menopausal Japanese women

Following the publication of the first Women's health Initiative report in 2002 that HRT may increase risk of developing breast cancer (19, 20), the HRT for the treatment of woman menstrual disorders has decreased dramatically in world-wide. As a result, many of women seek alternative or complementary strategies for menopausal symptoms.

Table 1. Age and anthropometric data of participants

	Maca treated participants (n=21)				Placebo treated participants (n=20)				*p* value	
	Baseline		8 weeks		Baseline		8 weeks		compared with placebo	
	mean	SE	mean	SE	mean	SE	mean	SE	Baseline	8 weeks
Age (years old)	50.0	0.9	50.0	0.9	48.4	1.0	48.4	1.0	0.245	0.245
Height (cm)	159.1	1.1	159.1	1.1	158.5	1.2	158.5	1.2	0.699	0.699
Weigt (kg)	52.5	1.8	52.7	1.8	55.0	1.4	54.6	1.5	0.275	0.418
BMI (kg/m2)	20.7	0.6	20.8	0.6	22.0	0.7	21.8	0.7	0.159	0.273
BFP (%)	23.7	1.2	24.1	1.3	25.5	1.2	24.8	1.2	0.283	0.660
Systolic BP (mmHg)	117.7	2.3	123.0	3.0	116.7	2.2	119.3	2.5	0.741	0.340
Diastolic BP (mmHg)	77.0	1.6	79.2	2.3	75.3	1.9	74.4	2.8	0.481	0.192
HR (bpm)	73.5	2.5	73.5	2.9	68.5	1.8	71.6	1.8	0.107	0.578

Data are given as mean and standard error.

Table 2. Effect of administration of Maca-BG1.2™ on serum hormones level

Hormone	Maca treated participants (n=21)				Placebo treated participants (n=20)				*p* value			
	Baseline		8 weeks		Baseline		8 weeks		compared with baseline		compared with placebo	
	mean	SE	mean	SE	mean	SE	mean	SE	Maca	Placebo	Baseline	8 weeks
LH (mIU/mL)	19.4	3.1	19.2	2.6	17.9	3.0	15.7	3.1	0.958	0.501	0.741	0.395
FSH (mIU/mL)	42.7	8.1	40.8	7.3	41.7	8.1	37.8	7.6	0.625	0.536	0.931	0.777
E2 (pg/mL)	78.9	17.7	112.7	36.3	67.5	18.2	50.9	11.5	0.326	0.258	0.657	0.118
PGS (ng/mL)	1.8	0.8	1.2	0.6	0.5	0.1	1.6	1.0	0.591	0.247	0.115	0.779

Data are given as mean and standard error.

Maca has been used for long time in the Andes to enhance fertility and treat menopausal discomfort and it is. Recent effective in animals (21) and humans (22).

In this study, we first report the effect of Maca treatment in peri-menopausal Japanese women. Our study indicates that it is safe to orally take 300 mg Maca-BG1.2™ daily for 8 weeks for Japanese women. In addition, Maca can significantly increase in the serum estradiol in women with regular menstruation and alleviate insomnia, one index of SMI, in women with mild menopausal disorder.

This is an important outcome because insomnia is one of two serious menopausal symptoms in Japanese meno-

Table 3. Effect of administraiton of Maca-BG1.2™ on serum hormones level of each menstruation condition group

Menstruation Cycle	Hormone	Maca treated participants (n=21)				Placebo treated participants (n=20)			
		Baseline		8 weeks		Baseline		8 weeks	
		mean	SE	mean	SE	mean	SE	mean	SE
Regular (n=10, each)	LH (mIU/mL)	11.0	4.1	12.3	3.5	8.5	2.8	9.7	4.4
	FSH (mIU/mL)	17.3	5.9	15.5	3.8	21.6	9.4	20.8	9.1
	E2 (pg/mL)	115.9	22.9	221.4	60.3	89.8	30.1	72.9	16.8
	PGS (ng/mL)	3.5	1.5	2.3	1.3	0.6	0.2	1.1	0.7
Irregular (n=4, each)	LH (mIU/mL)	26.5	5.9	23.8	5.9	24.7	5.4	15.7	8.1
	FSH (mIU/mL)	56.3	18.2	62.2	14.7	38.9	14.1	37.4	18.4
	E2 (pg/mL)	51.3	39.3	12.3	1.5	97.5	36.0	57.3	28.6
	PGS (ng/mL)	0.4	2.5	0.3	0.2	0.8	0.4	4.8	4.7
Stopped (menopause) (n=7, Maca, n=6, Placebo)	LH (mIU/mL)	27.2	4.5	26.4	3.1	29.1	4.2	25.8	2.9
	FSH (mIU/mL)	71.3	13.5	64.7	12.4	77.1	10.0	66.3	8.9
	E2 (pg/mL)	41.7	30.9	14.9	4.9	10.3	0.3	10.0	0.0
	PGS (ng/mL)	0.2	0.1	0.2	0.1	0.1	0.0	0.1	0.0

Menstruation Cycle	Hormone	*p* value			
		compared with baseline		compared with placebo	
		Maca	Placebo	Baseline	8 weeks
Regular (n=10, each)	LH (mIU/mL)	0.779	0.838	0.628	0.636
	FSH (mIU/mL)	0.755	0.946	0.700	0.595
	E2 (pg/mL)	0.109	0.482	0.499	0.038*
	PGS (ng/mL)	0.605	0.483	0.085†	0.404
Irregular (n=4, each)	LH (mIU/mL)	0.424	0.261	0.826	0.449
	FSH (mIU/mL)	0.461	0.911	0.478	0.332
	E2 (pg/mL)	0.381	0.447	0.418	0.213
	PGS (ng/mL)	0.278	0.411	0.479	0.400
Stopped (menopause) (n=7, Maca, n=6, Placebo)	LH (mIU/mL)	0.808	0.205	0.772	0.899
	FSH (mIU/mL)	0.431	0.037*	0.746	0.923
	E2 (pg/mL)	0.433	0.363	0.370	0.356
	PGS (ng/mL)	0.582	1.000	0.721	0.392

Data are given as mean and standard error. †marginally difference ($p<0.1$), *significantly difference ($p<0.05$).

pausal women. This result is different from the previous reports in postmenopausal women that Maca supplementation resulted in the improvement of anxiety and depression. The difference may depend on the difference of race, because anxiety and depression are not so serious menopausal symptoms in Japanese menopausal women. Thus, onset of menopausal symptoms may depend on biological and cultural variation.

Table 4. Effect of administration of Maca-BG1.2™ on SMI

	Maca treated participants (n=21)						Placebo treated participants (n=20)					
	Baseline			8 weeks			Baseline			8 weeks		
	Median	FQ	TQ	Median	FQ	TQ	Median	FQ	TQ	Median	FQ	TQ
Total SMI score	39.0	21.0	52.0	23.0	16.0	32.0	38.5	25.8	48.5	25.5	20.0	34.8
Hot Flushes	3.0	0.0	3.0	0.0	0.0	0.0	0.0	0.0	6.0	0.0	0.0	3.0
Sweats	3.0	3.0	6.0	3.0	0.0	3.0	3.0	3.0	7.0	3.0	0.0	6.0
Cold constitution	9.0	5.0	9.0	9.0	5.0	9.0	7.0	5.0	14.0	5.0	5.0	9.0
Shortness of breath or palpitation	0.0	0.0	4.0	0.0	0.0	4.0	4.0	0.0	5.0	0.0	0.0	4.0
Insomnia	5.0	0.0	5.0	0.0	0.0	5.0	5.0	0.0	9.0	5.0	0.0	9.0
Easy excitability or irritability	4.0	0.0	8.0	4.0	0.0	4.0	4.0	0.0	8.0	4.0	0.0	4.0
Worry about self depression	0.0	0.0	5.0	0.0	0.0	3.0	3.0	0.0	3.0	0.0	0.0	3.0
Headache, vertigo or nausea	0.0	0.0	3.0	0.0	0.0	3.0	1.5	0.0	3.0	0.0	0.0	3.0
Easy fatigability	2.0	2.0	4.0	2.0	2.0	4.0	4.0	2.0	4.0	2.0	2.0	4.0
Shoulder Stiffness, lumbago or joint pain	5.0	3.0	7.0	5.0	3.0	7.0	5.0	2.3	7.0	5.0	2.3	5.0

	p value			
	compared with baseline		compared with placebo	
	Maca	Placebo	Baseline	8 weeks
Total SMI score	0.013*	0.007**	0.725	0.754
Hot Flushes	0.078†	0.098†	0.696	0.505
Sweats	0.146	0.030*	0.558	0.571
Cold constitution	0.173	0.256	0.653	0.773
Shortness of breath or palpitation	0.345	0.010*	0.302	0.922
Insomnia	0.073†	0.877	0.615	0.052†
Easy excitability or irritability	0.143	0.095†	0.956	0.966
Worry about self depression	0.310	0.086†	0.746	0.767
Headache, vertigo or nausea	0.679	0.089†	0.696	0.691
Easy fatigability	0.021*	0.010*	0.480	0.734
Shoulder Stiffness, lumbago or joint pain	0.478	0.179	0.615	0.178

Data are given as median, FQ and TQ. †marginally difference ($p<0.1$), *significantly difference ($p<0.05$), **significantly difference ($p<0.01$).

Table 5. Effect of administration of Maca-BG1.2TM on SMI of each menopausal disorder severity group

Severity of menopausal disorder		Maca treated subjects						Placebo treated subjects						*p* value			
		Baseline			8 weeks			Baseline			8 weeks			compared with baseline		compared with placebo	
		Median	FQ	TQ	Median	FQ	TQ	Median	FQ	TQ	Median	FQ	TQ	Maca	Placebo	Baseline	8 weeks
Serious (n=6, Maca, n=5, Placebo)	Total SMI score	63.5	54.3	67.5	44.5	21.0	63.5	68.0	66.0	69.0	54.0	31.0	63.0	0.094†	0.125	0.358	0.662
	Hot Flushes	4.5	3.0	6.0	0.0	0.0	4.5	6.0	0.0	10.0	0.0	0.0	6.0	0.395	0.371	0.776	0.832
	Sweats	6.0	6.0	9.0	3.0	0.8	5.3	10.0	10.0	10.0	3.0	3.0	6.0	0.098†	0.098†	0.267	0.568
	Cold constitution	11.5	9.0	14.0	9.0	6.0	12.8	14.0	14.0	14.0	14.0	9.0	14.0	0.586	0.371	0.080†	0.434
	Shortness of breath or palpitation	6.0	4.0	8.0	4.0	0.0	8.0	4.0	0.0	8.0	0.0	0.0	4.0	0.345	0.371	0.565	0.539
	Insomnia	7.0	5.0	9.0	4.5	0.0	9.0	9.0	0.0	14.0	9.0	9.0	9.0	0.773	1.000	0.636	0.431
	Easy excitability or irritability	8.0	8.0	8.0	4.0	4.0	7.0	8.0	4.0	8.0	4.0	4.0	8.0	0.089†	0.371	0.614	0.922
	Worry about self depression	5.0	3.5	5.0	1.5	0.0	3.0	3.0	3.0	5.0	3.0	3.0	3.0	0.100	0.174	0.773	0.431
	Headache, vertigo or nausea	3.0	3.0	4.5	1.5	0.0	4.5	3.0	0.0	3.0	0.0	0.0	3.0	0.346	0.586	0.434	0.686
	Easy fatigability	5.5	4.0	7.0	4.0	2.5	4.0	4.0	4.0	7.0	4.0	4.0	4.0	0.098†	0.371	0.752	0.525
	Shoulder Stiffness, lumbago or joint pain	7.0	7.0	7.0	6.0	5.0	7.0	7.0	7.0	7.0	5.0	5.0	5.0	0.174	0.072†	NA	0.609
Mild (n=15, each)	Total SMI score	28.0	19.5	39.5	23.0	15.5	28.0	31.0	21.5	40.0	23.0	17.5	29.5	0.084†	0.044*	0.506	0.884
	Hot Flushes	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	3.0	0.0	0.0	3.0	0.037*	0.374	0.889	0.453
	Sweats	3.0	1.5	3.0	3.0	0.0	3.0	3.0	1.5	6.0	3.0	0.0	4.5	1.000	0.281	0.578	0.707
	Cold constitution	9.0	5.0	9.0	5.0	5.0	9.0	5.0	5.0	9.0	5.0	5.0	9.0	0.234	0.715	0.189	0.565
	Shortness of breath or palpitation	0.0	0.0	0.0	0.0	0.0	0.0	4.0	0.0	4.0	0.0	0.0	2.0	NA	0.026*	0.033*	0.694
	Insomnia	0.0	0.0	5.0	0.0	0.0	0.0	5.0	0.0	5.0	5.0	0.0	5.0	0.072†	1.000	0.407	0.041*
	Easy excitability or irritability	0.0	0.0	4.0	0.0	0.0	4.0	4.0	0.0	4.0	4.0	0.0	4.0	0.850	0.299	0.638	0.908
	Worry about self depression	0.0	0.0	3.0	0.0	0.0	3.0	0.0	0.0	3.0	0.0	0.0	1.5	0.892	0.414	0.942	0.411
	Headache, vertigo or nausea	0.0	0.0	1.5	0.0	0.0	3.0	0.0	0.0	3.0	0.0	0.0	3.0	0.586	0.181	0.263	0.900
	Easy fatigability	2.0	2.0	3.0	2.0	1.0	2.0	4.0	2.0	4.0	2.0	2.0	2.0	0.203	0.020*	0.163	0.570
	Shoulder Stiffness, lumbago or joint pain	3.0	3.0	5.0	5.0	3.0	5.0	3.0	0.0	5.0	3.0	0.0	5.0	0.821	0.660	0.604	0.211

Data are given as median, FQ and TQ. †marginally difference ($p<0.1$). *significantly difference ($p<0.05$); NA, not available.

Hypothetical Mechanism of Maca to improve insomnia

Well known insomnia related nutrients are tryptophan, gamma-aminobutyric acid (GABA), calcium, potassium and so on (23). We analyzed and saw that Maca-BG1.2™ contains GABA (approx. 300 mg/100 g) and potassium (approx. 900 mg/100g) (data not shown).

In addition, Maca-BG1.2™ was confirmed to contain one of the benzylalkamide, called macamide, *N*-(3-methoxybenzyl)-(9*Z*, 12*Z*)-octadecadienamide (approx. 2 mg/100 g, data not shown). Some macamide are known to inhibit fatty acid amide hydrolase (FAAH) (24) which catalyzes the hydrolysis of anandamide, a sleep promoting and wakefulness reducing endocannabinoid. GABA, potassium and macamide may act synergistically to improve insomnia but many are remained to be uncovered yet. Because there are many insomnia persons in Japan and, unfortunately, in the world, Maca-BG1.2™ may be useful for many people.

REFERENCES

1. Dailey RK, *et al*. Herbal product use and menopause symptom relief in primary care patients: a Metro Net study. *J. Women's Health*. 2003; 12: 633-641.
2. Shirota T, *et al*. A survey of patients with menopausal symptoms on Complementary and Alternative Medicine (CAM) at the St. Marianna University Hospital. J. Jpn. Menopause Soc. 2003; 11: 13-18.
3. Miyahara F. Health promotion system for Japanese women among menopausal generation. Obstet. Gynecol. Ther. 2004; 88: 1194-1200.
4. Gonzales GF. Maca: Del Alimento Perdido de los Incas al Milagros de los Andes. Estudio de Seguridad Alimentaria y Nutricional. Segurança Alimentar e Nutricional, Campinas. 2010; 17: 16-36.
5. Guo SS, *et al*. Preservation of Cognitive Function by Lepidium meyenii (Maca) Is Associated with Improvement of Mitochondrial Activity and Upregulation of Autophagy-Related Proteins in Middle-Aged Mouse Cortex. Evid. Based Complement. Alternat. Med. 2016; 2016: 4394261.
6. Cicero AF, *et al*. Lepidium meyenii Walp. improves sexual behaviour in male rats independently from its action on spontaneous locomotor activity. J. Ethnopharmacol. 2001; 75: 225-229.
7. Clément C, *et al*. Effect of maca supplementation on bovine sperm quantity and quality followed over two spermatogenic cycles. Theriogenology. 2010; 74: 173-183.
8. Zhang Y, *et al*. Effect of ethanol extract of Lepidium meyenii Walp. on osteoporosis in ovariectomized rat. J. Ethnopharmacol. 2006; 105: 274-279.
9. Meissner HO, *et al*. Hormone-Balancing Effect of Pre-Gelatinized Organic Maca (Lepidium peruvianum Chacon): (I) Biochemical and Pharmacodynamic Study on Maca using Clinical Laboratory Model on Ovariectomized Rats. Int. J. Biomed. Sci. 2006; 2: 260-272.
10. Stone M, *et al*. A pilot investigation into the effect of maca supplementation on physical activity and sexual desire in sportsmen. J. Ethnopharmacol. 2009; 126: 574-576.
11. Melnikovova I, *et al*. Effect of Lepidium meyenii Walp. on Semen Parameters and Serum Hormone Levels in Healthy Adult Men: A Double-Blind, Randomized, Placebo-Controlled Pilot Study. Evid. Based Complement. Alternat. Med. 2015; 2015: 324369.
12. Meissner HO, *et al*. Hormone-Balancing Effect of Pre-Gelatinized Organic Maca (Lepidium peruvianum Chacon): (III) Clinical responses of early-postmenopausal women to Maca in double blind, randomized, Placebo-controlled, crossover configuration, outpatient study. Int. J. Biomed. Sci. 2006; 2: 375-394.
13. Brooks NA, *et al*. Beneficial effects of Lepidium meyenii (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content. Menopause. 2008; 15: 1157-1162.
14. Stojanovska L, *et al*. Maca reduces blood pressure and depression, in a pilot study in postmenopausal women. Climacteric. 2015; 18: 69-78.
15. Valentová K, *et al*. The in vitro biological activity of Lepidium meyenii extracts. Cell Biol. Toxicol. 2006; 22: 91-99.
16. Yi F, *et al*. In silico profiling for secondary metabolites from Lepidium meyenii (maca) by the pharmacophore and ligand-shape-based joint approach. Chin. Med. 2016; 11: 42.
17. Ikeda H, *et al*. Effects of candesartan for middle-aged and elderly women with hypertension and menopausal-like symptoms. Hypertens. Res. 2006; 29: 1007-1012.
18. Koyama T and Asou T. Kohnenki fujin ni okeru Kampo chiryoh: Kanryakuka sita kohnenki shisuh ni yoru hyohka. (Treatment of Chinese medicine in Japanese menopausal women: Evaluation by simplified menopausal index.) Recent Progress of Kampo Medicine in Obstetrics and Gynecology. 1992; 9: 30-34.
19. McDonough PG. The randomized world is not without its imperfections: reflections on the Women's Health Initiative Study. Fertil. Steril. 2002; 78: 951-956.
20. Burger HG, *et al*. Evidence-based assessment of the impact of the WHI on women's health. Climacteric. 2012; 15: 281-287.
21. Zhang Y, *et al*. Effect of ethanolic extract of Lepidium meyenii Walp on serum hormone levels in ovariectomized rats. Indian J. Pharmacol. 2014; 46: 416-419.
22. Stojanovska L, *et al*. Maca reduces blood pressure and depression, in a pilot study in postmenopausal women. Climacteric. 2015; 18: 69-78.
23. Zeng Y, *et al*. Strategies of Functional Foods Promote Sleep in Human Being. Curr. Signal Transduc. Ther. 2014; 9: 148-155.
24. Wu H, *et al*. Macamides and their synthetic analogs: Evaluation of in vitro FAAH inhibition. Bioorg. Med. Chem. 2013; 21: 5188-5197.