Menopause: The Journal of The North American Menopause Society
Vol. 15, No. 6, pp. 1157-1162
DOI: 10.1097/gme.0b013e3181732953

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

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Abstract

Objective: To examine the estrogenic and androgenic activity of *Lepidium meyenii* (Maca) and its effect on the hormonal profile and symptoms in postmenopausal women.

Design: Fourteen postmenopausal women completed a randomized, double-blind, placebo-controlled, crossover trial. They received 3.5 g/day of powered Maca for 6 weeks and matching placebo for 6 weeks, in either order, over a total of 12 weeks. At baseline and weeks 6 and 12 blood samples were collected for the measurement of estradiol, follicle-stimulating hormone, luteinizing hormone, and sex hormone–binding globulin, and the women completed the Greene Climacteric Scale to assess the severity of menopausal symptoms. In addition, aqueous and methanolic Maca extracts were tested for androgenic and estrogenic activity using a yeast-based hormone-dependent reporter assay.

Results: No differences were seen in serum concentrations of estradiol, follicle-stimulating hormone, luteinizing hormone, and sex hormone–binding globulin between baseline, Maca treatment, and placebo ($P > 0.05$). The Greene Climacteric Scale revealed a significant reduction in scores in the areas of psychological symptoms, including the subscales for anxiety and depression and sexual dysfunction after Maca consumption compared with both baseline and placebo ($P < 0.05$). These findings did not correlate with androgenic or α-estrogenic activity present in the Maca as no physiologically significant activity was observed in yeast-based assays employing up to 4 mg/mL Maca extract (equivalent to 200 mg/mL Maca).

Conclusions: Preliminary findings show that *Lepidium meyenii* (Maca) (3.5 g/d) reduces psychological symptoms, including anxiety and depression, and lowers measures of sexual dysfunction in postmenopausal women independent of estrogenic and androgenic activity.

Key Words: *Lepidium meyenii* – Maca – Menopausal symptoms – Anxiety – Depression – Complementary therapies – Estrogenicity.

Received January 22, 2008; revised and accepted March 10, 2008.

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Funding/support: Dr. Cox is supported in part by grant 5G12RR008124 (to the Border Biomedical Research Center/University of Texas at El Paso) from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NCRR or NIH. The Biomolecule Analysis Core Facility is supported by NIH/NCRR grant 5G12RR008124.

Financial disclosure: None reported.

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Hormone therapy (HT) is the most effective treatment for the relief of menopausal symptoms, yet many women have become reluctant to continue and/or commence HT because of unwanted side effects or fear of adverse risks.[1] Instead women seek alternative treatment options,[2] particularly complementary and alternative therapies.[3] A recent study conducted in Australian women revealed that more than 50% of respondents had used complementary and alternative medicine (CAM) and/or visited a CAM practitioner for the alleviation of menopausal symptoms within the past 12 months.[4] Furthermore, after the release of the Women's Health Initiative study findings indicating that HT was associated with adverse health risks,[5] there has been an increase in the number of dietary supplements manufactured specifically targeting menopausal women.[6]

Many alternative therapies currently available claim to provide a wide array of benefits for menopausal women, of which some, including soy and black cohosh, have been supported by scientific evidence.[2,6] There are, however,

numerous products for which benefit has been claimed, but scientific support is lacking.[3] Maca is one example. Maca is the root of the plant *Lepidium meyenii*, which is grown exclusively at high altitude in the Andean region of Peru where it is widely used for its putative fertility-enhancing and aphrodisiac properties.[7,8]

Maca is marketed commercially for its reported benefit in relieving menopausal symptoms, although there are scant published scientific data to support any efficacy.[9] Initial research has focused on a possible role for Maca in improving male fertility,[10-20] with emerging evidence that Maca may improve sperm production.[10] Although few studies have as yet examined the effect of Maca in women, data from ovariectomized rats suggest that Maca can improve bone mass and restore trabecular network in the lumbar vertebrae, findings relevant to the high risk of osteoporosis that many women face after menopause.[21]

The mechanisms by which Maca may affect the male or female reproductive system remain to be elucidated. The possibility of estrogenic effects is based on the fact that Maca contains the phytoestrogen β-sitosterol.[19] Several studies, however, have been unable to detect in vivo estrogenic effects,[13,14,16,19] although one study has reported that Maca extracts promote proliferation of MCF-7 cells, an estrogen receptor–positive human breast cancer cell line.[22] Alkaloids, isothiocyanates, and glucosinolates are also potential active constituents of Maca.[21] One constituent, glucosinolate indoly-3-methyl (glucobrassicin), may modulate androgenic activity as it can be enzymatically hydrolyzed to 3,3-diindolylmethane, known as a specific antagonist of the androgen receptor.[23-25] To our knowledge, 3,3-diindolylmethane is the first example of a pure androgen receptor antagonist from plants.[25]

This study sought to examine the estrogenic and androgenic activity of *Lepidium meyenii* (Maca) and its effect on the hormonal profile and symptoms in postmenopausal women. In a randomized, crossover study, serum sex hormone levels and sex hormone–binding globulin (SHBG) concentrations were measured in 16 postmenopausal women. Furthermore, as women often report that Maca is beneficial in alleviating menopausal symptoms, changes in menopausal symptoms were also examined in our study using the Greene Climacteric Scale (GCS), a well-validated questionnaire.

METHODS

Preparation of Maca extracts

Dried Maca powder (Maca Power, Incan Food, Murwillumbah, NSW, Australia) was used for this study. To determine active ingredients, 5 g of this powder was macerated with 50 mL of distilled water and stirred overnight. The aqueous extract was then filtered through a Whatman glass microfiber filter, freeze dried, and stored at −80°C. This aqueous extract was thawed and resuspended in distilled water before assay. Maca powder remaining after aqueous extraction was macerated with 50 mL of methanol and allowed to stir overnight. The methanolic extract was filtered with a Whatman glass microfiber filter and dried on a rotovap. Dried methanolic extracts were then resuspended in dimethylsulfoxide (DMSO) before assaying because the extract was not completely soluble in ethanol and methanol is toxic to yeast. The yeast used in the assays described below can tolerate up to 1% DMSO without discernible effects on yeast cell growth.

Estrogenic and androgenic activity measures

The yeast β-galactosidase reporter assays (used as a quantitative indicator of steroid hormone receptor activity), the yeast strain W303a, the androgen-inducible β-galactosidase reporter plasmid (pUCΔS-26X), and the human androgen receptor expression plasmid were as previously described.[26,27] The human estrogen receptor α expression plasmid and the estrogen-inducible reporter plasmid were gifts from Didier Picard (University of Geneva, Switzerland). W303a was cotransformed with two plasmids: a constitutive androgen or estrogen receptor expression plasmid and a hormone-inducible β-galactosidase reporter plasmid. The hormone induction protocol used here was modified to a 96-well plate format. In short, yeast cultures in exponential phase growth were aliquoted at 100 μL per well into an opaque 96-well plate. The wells were treated with the indicated concentrations of hormone as a positive control or the Maca extracts for 2 hours. Hormone and Maca extract concentrations were prepared so that all wells received exactly 1% DMSO. The wells were then treated with the chemiluminescent substrate, incubated for 2 hours at room temperature, and measured on a microplate luminometer (Luminoskan Ascent, LabSystems) as described previously.[26,27]

Participants

Sixteen healthy postmenopausal women ages 50 to 60 years who were currently experiencing symptoms of menopause, recruited by community advertisement, participated in this study. All women reported being amenorrheic for 12 months or more and reported experiencing fatigue, lack of energy, difficulty in sleeping, and hot flushes of moderate severity. These self-reported symptoms, however, were not confirmed by questionnaire until after study commencement. Women were excluded from the study if they were currently taking HT or had taken HT within the past 6 months; if they had a cardiac, renal, hepatic, inflammatory, or psychiatric conditions; or if they regularly consumed more than two standard alcoholic drinks each day. Women were also excluded if they currently consumed Maca supplements or any other nutritional or alternative medicine supplements for the relief of menopausal symptoms. Women were required not to consume any dietary supplements or other alternative herbal therapies for the duration of the study.

Study design

The study protocol was approved by the Human Research Ethics Committee of Victoria University, and written informed consent was obtained from all participants. The study was designed as a randomized, double-blind, placebo-controlled, crossover trial. Fourteen of the 16 women recruited

for the study completed the trial. Seven women commenced the placebo treatment first and seven women commenced the Maca treatment first. Each woman received 3.5 g/d of powered Maca or placebo for 6 weeks, in random order, with the entire study extending over a period of 12 weeks. The dose of 3.5 g/d was based on previous human studies.[12,13]

At baseline and weeks 6 and 12, venous blood samples were collected from the antecubital vein for the measurement of serum estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and SHBG. At baseline and weeks 6 and 12, women also completed the GCS to determine whether there had been any change in the severity of their menopausal symptoms. Height and body weight were also determined at these three time points. Maca was obtained in powder form (Maca Power, Incan Food) and given to subjects in preweighed 3.5-g amounts in plastic sachets. A placebo powder of matching color and consistency (refined white rice flour) was provided in an identical dose. Subjects were asked to consume one 3.5-g dose of Maca or placebo per day, taken in their breakfast cereal, in a soup, or in a milk shake.

Measurements

Serum estradiol, FSH, LH, and SHBG were analyzed by a commercial pathology laboratory (Melbourne Pathology, Melbourne, Australia). Serum estradiol was determined by an electrochemiluminescent immunoassay using the Elecsys Estradiol II reagent kit (Roche Diagnostics, Indianapolis, IN). Inter- and intra-assay coefficient variations were 3.3% and 6.2%, respectively. FSH and LH were determined by a chemiluminescent microparticle immunoassay using Architect FSH and Architect LH kits, respectively (Abbott Laboratories, Abbott Park, IL). Inter- and intra-assay coefficient variations were 3.0% and 3.4% for FSH and 2.1% and 3.3% for LH, respectively. All three hormonal assays were performed using the Modular Analytics E170 immunoassay analyzer (Roche Diagnostics).

SHBG was determined using a two-site chemiluminescent immunometric assay measured on the Immulite 2000 advanced immunoassay system (Diagnostic Products Corporation, Los Angeles, CA). Intra- and inter-assay coefficient variations for the SHBG assay were 6.5% and 8.7%, respectively.

The GCS is a well-validated, nonintrusive self-report questionnaire that measures the physical and psychological symptoms associated with menopause. The scale assesses psychological symptoms, with subscales for anxiety and depression, somatic symptoms, vasomotor symptoms, and sexual dysfunction. A total score is also calculated.[28] Test reliability for the subscales ranges from 0.83 for the vasomotor scale to 0.87 for the psychological scale.[28,29]

Statistical analysis

Statistical analyses were performed using SPSS (version 15.0, SPSS Inc., Chicago, IL). All data are expressed as the mean ± SD.

Data were first assessed for normality using the Kolmogorov-Smirnov test. Analyses of hormone levels, GCS, and body weight were performed using one-way repeated-measures analysis of variance with Tukey honestly significant difference as a post hoc analysis. A P value of <0.05 was considered of statistical significance. Analyses of variance using treatment order as a between-subjects factor indicated that there was no carryover effect in any of the measured variables.

RESULTS

Estrogenic and androgenic activity

Dried Maca powder was extracted with distilled water followed by extraction with methanol. Extraction yields of 58% (aqueous) and 2% (methanol) were obtained. Both the aqueous and methanolic extracts were assayed for the ability to induce androgen and estrogen receptor–mediated β-galactosidase reporter expression. An example of the estrogenic activity screen of the Maca methanolic extracts is illustrated in Figure 1. The data obtained for the estrogenic activity screen of the aqueous extract and in the androgenic activity screens were identical. The mean effective concentration for estradiol and dihydrotestosterone, which were used as positive controls in the hormone activity screens, were 1.66 nM (Fig. 1A) and 43 nM (data not shown), respectively. We did not detect any estrogenic (Fig. 1B) or androgenic (data not shown) activity in the methanolic extracts up to a concentration of 4 mg/mL. Based on the original starting material and the amount of extract used, this corresponds to 200 mg/mL Maca. Similar results were obtained with the aqueous extracts (data not shown). Higher concentrations of extract cannot be tested because the dark color of the extract interferes with the assay. Given the lack of activity at the concentrations tested, however, it is safe to conclude that no physiologically significant estrogenic or androgenic activity was present in the Maca preparation used in this study.

Study population

Of the initial 16 women recruited, two failed to complete the study due to time constraints. Data have therefore been

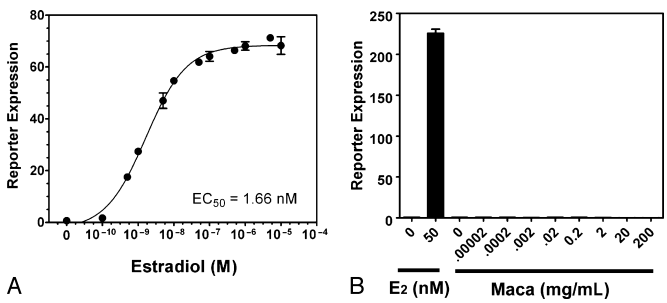

FIG. 1. Yeast-based estrogenic activity screen of methanolic Maca extracts. **A:** An estradiol dose response was obtained in the estrogen-responsive yeast reporter strain. Estrogenic activity is detected down to an estradiol concentration of 100 pM. The mean effective concentration for estradiol in this assay is 1.66 nM. **B:** A dose response similar to that shown in **A** was obtained with the Maca methanolic extract. Estradiol at 0 and 50 nM was used as a control. No estrogenic activity was detected in the Maca extract up to 200 mg/mL Maca. The concentrations shown on the graph were calculated based on the weight of the original starting material and the amount of extract used and are representative of the total Maca rather than the amount of extract. All data are reported as mean ± SD and are representative of three replicate wells.

TABLE 1. *Body weight (kg) during the randomized, crossover study (n = 14)*

Treatment order	Baseline	6 wk	12 wk
Maca then placebo (n = 7)	75.5 ± 22.6	75.3 ± 23.1	75.6 ± 22.3
Placebo then Maca (n =7)	76.7 ± 14.2	76.9 ± 14.5	76.7 ± 14.4

analyzed for a total of 14 women. These women had mean (± SD) age of 53.5 (± 10.8) years at the start of the study and were overweight (mean body mass index 27.1 ± 1.8 kg/m^2). Both body weight (kg) and body mass index did not change significantly during the study (Table 1).

Hormone profile

Serum hormone levels of estradiol, FSH, LH, and SHBG were measured at baseline and at 6 and 12 weeks (Table 2). No statistically significant changes in serum hormone levels or SHBG were found ($P > 0.05$). Post hoc analyses show, however, that our study is only powered to detect as significant (at $P = 0.08$ and $\alpha = 0.05$) a 30% increase in estradiol.

GCS

Figure 2 presents results from the GCS. The psychological scale indicated that Maca treatment was associated with a significant reduction in symptom scores (30% reduction from baseline values, $P < 0.05$) and values after treatment with placebo (27% less than after placebo, $P < 0.05$). The psychological scale contained two subgroups, anxiety and depression. Results for the anxiety scale show a significant reduction in scores after Maca treatment compared with baseline (30.8% reduction, $P < 0.05$) and values after treatment with placebo (27.3% decrease, $P < 0.05$). The second subscale measured depression, where again a significant reduction in scores was seen after Maca compared with either baseline or after placebo (28.9% and 26.8%, respectively, both $P < 0.05$).

A significant decrease was also observed in the sexual problems domain where scores after Maca intake were 22.9% and 34.6%, respectively, below those reported at baseline and after placebo (both $P < 0.05$).

The GCS also allows for a total score to be calculated. Maca significantly decreased total scores by 18.0% compared with baseline ($P < 0.05$). Additionally a significant reduction of 17.3% was also shown between Maca treatment compared with placebo ($P < 0.05$). There were no significant changes seen in somatic or vasomotor scores during the trial.

DISCUSSION

This study set out to determine the effect of consuming *Lepidium meyenii* (Maca) in postmenopausal women. Maca was shown to have significant effects on psychological symptoms including effects on anxiety and depression as measured by the GCS and its subscales (Fig. 2). This is an important finding given that women in the menopausal transition are up to three times more likely to report depressive symptoms than premenopausal women.[30] Additionally, Maca appeared to significantly reduce sexual problems (Fig. 2). These changes do not appear to have an endocrine basis since no change was evident in sex hormones or SHBG (Table 2). To our knowledge, this is the first study to demonstrate these potential psychological benefits of Maca in menopausal women.

Our finding that a 6-week treatment with Maca caused no hormonal changes in postmenopausal women is consistent with the studies of Gonzales et al[13] who also showed in males given Maca 1.5 or 3.0 g/d for 12 weeks that Maca therapy had no effect on serum estradiol, FSH, or LH levels. Moreover, we also demonstrated that no estrogenic and androgenic activity could be extracted from the Maca preparation used in this study. It remains possible that a small amount of estrogenic and/or androgenic activity below detection limits was present in our Maca preparations. However, it is highly unlikely that such low activity levels would influence the physiological and psychological parameters that were observed. The absence of hormonal effects fails to support the proposal[12,23] that the action of Maca is related to the phytoestrogenic activity of β-sitosterol. Moreover, it is known that β-sitosterol, like other sterols, is poorly absorbed in humans.[31] Our results are not, therefore, in agreement with those of Meissner et al[9] who reported elevated LH and reduced FSH levels after Maca treatment for 12 weeks in a cohort of early postmenopausal women. Although the active ingredient remains uncertain, given the limited data available on Maca, it is likely that many variables are of importance. Notably, the dose given, type of commercial preparation used, the species or variety of *Lepidium* from which preparations are derived, and extraction protocols and delivery mechanisms employed may all influence the efficacy of Maca treatment. Given the unregulated nature of complementary therapies, there is a propensity for preparations to contain varying amounts of active ingredients.[32]

Our results for the changes induced by Maca in psychological symptoms, particularly depression and anxiety, are supported by other studies. Gonzales et al[13] found that in men, treatment with Maca lowered depression scores. In addition, Rubio et al[33] found that in ovariectomized mice, immobility time in the forced swimming test, a validated method for determining possible antidepressant actions of a drug, were reduced in mice fed Maca.

It is difficult to postulate how Maca is acting to reduce psychological symptoms, given the complex nature of psychological control. There is evidence to indicate that

TABLE 2. *Mean values of serum estradiol, FSH, LH, and SHBG at baseline, after Maca, and after placebo*

	Baseline	After 6 wk of Maca	After 6 wk of placebo
Estradiol (pmol/L)	65.1 ± 18.8	60.6 ± 13.7	62.0 ± 17.7
FSH (IU/L)	60.1 ± 22.1	63.9 ± 23.6	63.7 ± 23.7
LH (IU/L)	30.6 ± 13.8	31.1 ± 12.0	32.5 ± 13.5
SHBG (nmol/L)	44.3 ± 23.0	42.4 ± 22.6	43.9 ± 22.5

Data are the mean ± SD (n = 14). FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone–binding globulin.

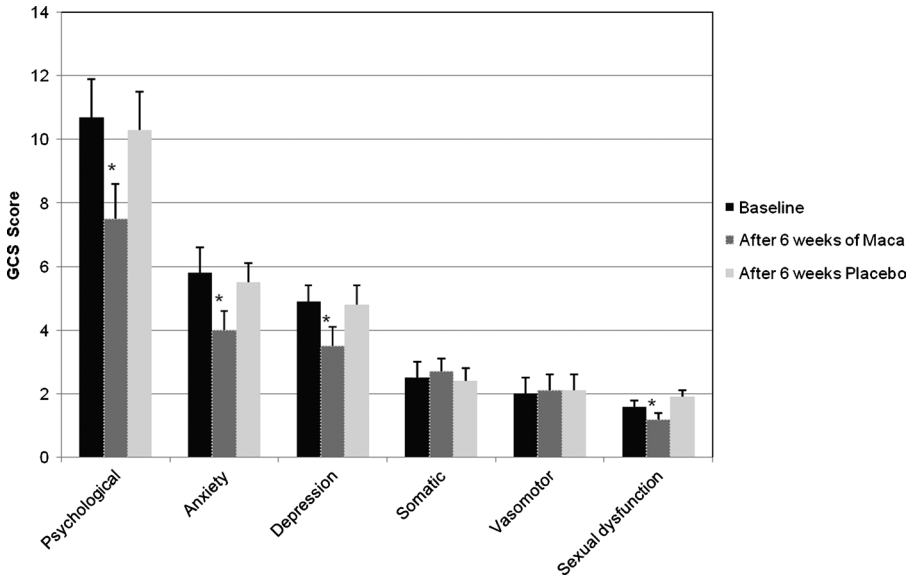

FIG. 2. Mean scores on the Greene Climacteric Scale (GCS) at baseline, after Maca, and after placebo. Error bars represent the SEM. *Significant difference from baseline and placebo ($P < 0.05$).

flavonoids present in Maca are potent inhibitors of monoamine oxidase activity, thus mimicking the actions of monoamine oxidase antidepressant medication.[34,35] Sloley et al[35] demonstrated that in vitro Ginkgo biloba extract inhibits monoamine oxidase, principally due to the flavonoid kaempferol, which is also known to be present in Maca. However, the specific role of flavonoids in Maca remains to be established.[33,36]

An interesting finding of this study was that the decrease in psychological symptoms was not associated with any decrease in vasomotor symptoms (Fig. 2). This is despite several studies[37,38] showing a strong association between anxiety and depression and the prevalence of hot flushes. Furthermore, this is in contrast to the apparent actions of isoflavones, which may improve vasomotor but not mood symptoms.[2] These results support the notion of a direct effect of Maca on psychological symptoms as opposed to an indirect effect resulting from an improvement in vasomotor symptoms, sleep, and therefore mood.

A further finding of this study is that Maca significantly decreased scores indicative of sexual problems (Fig. 2). Again, these results are consistent with previous research conducted in men[13] and also in rodents.[20] Menopausal women are known to report a high prevalence of sexual problems. Dennerstein et al[39] found that although 42% of menopausal women had scores indicative of sexual difficulties as these women became postmenopausal, the prevalence of these problems reached 88%. Although it is plausible that a decrease in sexual problems may occur via an indirect method such as improvement in psychological function, Gonzales et al[13] have noted that improvement in sexual desire is independent of any effect on anxiety and/or depression.

Our results are of a preliminary nature and need confirmation in studies using a larger sample size and in women at different stages of the menopausal transition. Potential effects of Maca on anxiety and depression should also be studied with the use of specific psychological scales in other groups in whom these symptoms are prevalent. In addition, it will be necessary to elucidate the mechanisms of Maca action.

CONCLUSIONS

In summary, we revealed that Maca does not exert an estrogenic effect in postmenopausal women, as indicated by the lack of change in plasma estradiol, FSH, LH, and SHBG concentrations. However, Maca was shown to be effective in reducing psychological symptoms, including anxiety and depression, along with sexual dysfunction associated with menopause.

Acknowledgments: We thank the Biomolecule Analysis Core Facility for the use of the instruments. We are grateful to Anne Lise Tang for her input into this study.

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