

Clinical Effects of a Proprietary, Standardized, Concentrated, Organic *Lepidium Peruvianum* Formulation (Maca-GO®) as an Alternative to HRT

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Introduction

Women going through menopause may experience a variety of symptoms, ranging from hot flashes and night sweats to sleep disturbances, mood disorders, loss of sexual desire, and vaginal dryness.¹ Hormone replacement therapy (HRT), using estrogen or a combination of estrogen and a progestin has increasingly been the therapy of choice for relieving menopause-related symptoms in Western cultures for many decades.

However, several large clinical trials—and in particular the Women’s Health Initiative (WHI)—found an increased risk of developing serious health problems caused or stimulated by HRT such as stroke and breast cancer in women using estrogen and estrogen-progestin HRT. Not surprisingly, women have become increasingly reluctant to use HRT for menopausal symptoms. Thus the search for alternative options.²

Lepidium, commonly known as the peppergrasses or pepperworts, is a genus of plants in the mustard family Brassicaceae. Two names (*Lepidium peruvianum* Chacon and *Lepidium meyenii* Walpers) still populate the scientific literature addressing the same species of *Lepidium*, commonly known as “Maca.”

To foster a culture of respect for scientific investigation and legitimacy, an authoritative plant taxonomy specialists’ work group—that included the Peruvian Government, La Molina University and San Marcos University—recently, officially, and by consensus recognized the true species denominated with the common name “Maca” with the scientific name ***Lepidium peruvianum Chacon*** (“*Lepidium peruvianum*” in this document)—in accordance to the rules of the International Code of Botanical Nomenclature.³

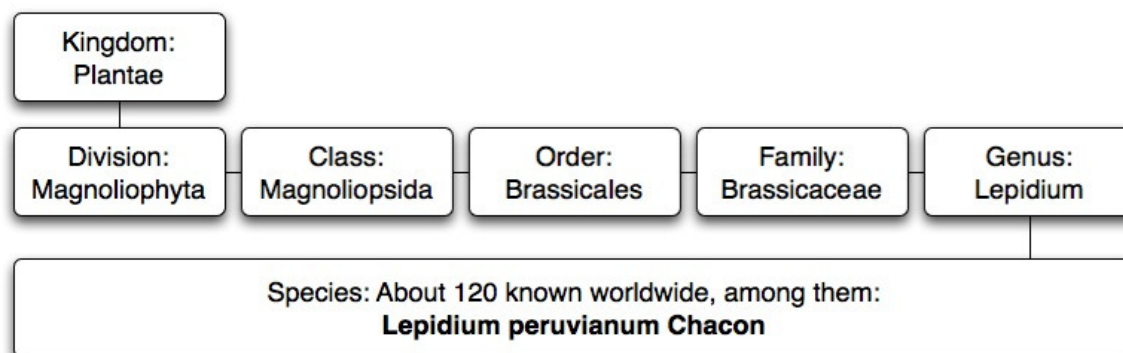


Figure 1: Scientific classification of *Lepidium peruvianum Chacon*.

Lepidium peruvianum is thus a *Lepidium* species native to Peru that grows in areas where human groups have lived as far back as 4,000 years ago. *Lepidium peruvianum* is one of about 14 identified *Lepidium* species that only grows at high altitudes and is the only one known for its fertility-enhancing properties, energizing effects, and high nutritional value.^{4,5,6,7}

The purpose of this paper is to report and discuss key findings of a European multi-center, double-blind, randomized, placebo-controlled trial—the first study of a standardized, concentrated *Lepidium peruvianum* formulation (Maca-GO®) in menopausal women—to propose the use of *Lepidium peruvianum* as a non-hormonal alternative to hormone replacement therapy (HRT).

Standardized Concentrated Lepidium Peruvianum Formulations Maca-GO® and Maca-OG™

Reported medicinal properties and energizing effects of *Lepidium peruvianum* are linked to the peculiar composition of this plant—cultivated exclusively in the central Peruvian Andes at 12-14,000 feet, under harsh natural conditions, exposed to the full spectrum of solar radiation, low humidity and extreme temperature changes.¹⁵

Beneficial properties of *Lepidium peruvianum* were first linked to alkaloids identified in the 1960's by Chacon.⁴ In recent years, other groups of active constituents were reported, such as polyunsaturated acids and their amides, plant sterols such as stigmasterol, one of a group of phytosterols that includes campesterol, ergosterol (provitamin D2) and brassicasterol—all biochemically related to cholesterol and steroid hormones such as estrogen, testosterone and progesterone—and aromatic glucosinolates such as benzyl and p-methoxybenzyl glucosinolates, and their derived isothiocyanates.^{8,21,9,10,11}

Lepidium peruvianum can be regarded as an adaptogen—an agent that supports homeostasis by priming the body to better endure adverse stressors. Adaptogens raise overall nonspecific resistance leading the organism to better adapt to stressful circumstances,¹² i.e. reducing or eliminating the exhaustion phase that follows a typical stress response.

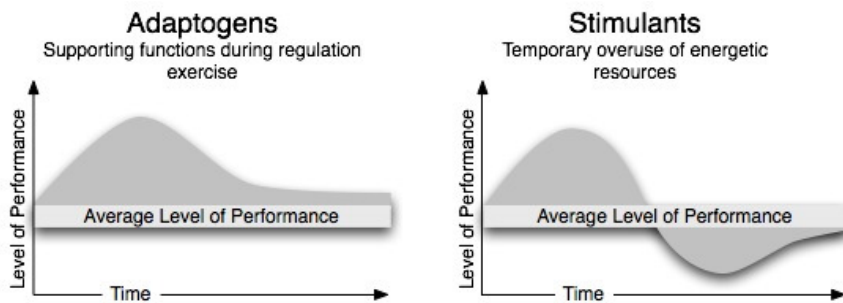


Figure 2: Difference between an adaptogen and a stimulant. An adaptogen primes the organism with energy reserves to deal with stressors. A stimulant increases the body's ability to respond to a stressor, followed by an exhaustion phase in which energy reserves are depleted and need to build up again.

The species *Lepidium peruvianum* consists of 13 different subspecies or phenotypes. Each phenotype is of a characteristic color and displays varying distribution patterns of active constituents. No active constituent, taken alone, has been found to be *Lepidium peruvianum*'s single functional marker for its claimed benefits.¹³ Moreover, different phenotypes have shown diverse physiological effects and gender-affinity—thereby giving rise to two different *Lepidium peruvianum* products, Maca-GO® (Femmenessence™) for women, and Maca-OG™ (Revolution) for men.

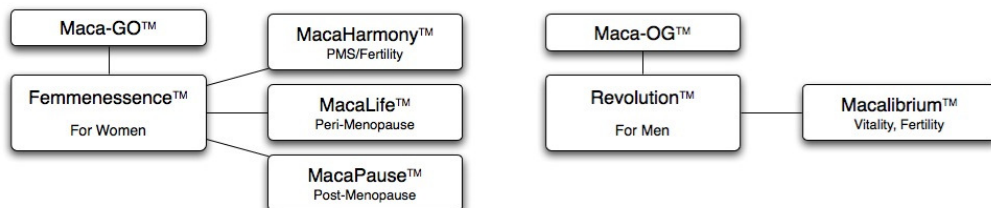


Figure 3: Product line with standardized formulations based on *Lepidium peruvianum*: Maca-GO™ and Maca-OG™

Maca-GO® (for women) and Maca-OG™ (for men) are proprietary formulations made from certified organic *Lepidium peruvianum* phenotypes that go through a patented (Patent Pending US Application Serial No. 60/819,583) manufacturing process that includes pre-gelatinization to achieve optimized, increased concentrations of all of the plant's known functional constituents (see Figure 4).^{14,15}

Natural Health International's proprietary process includes quality-enhancement procedures starting with careful selection of soil and growing locations, seed selection, cultivation and harvest methods. Ozone, low temperature, controlled pressure and moisture—as opposed to radiation, solvents, and high heat—are used in the patent pending (U.S. No. 60/819,583) process to sterilize, unlock the bioavailability, and concentrate *Lepidium peruvianum's* entire spectrum of active constituents in the gender-specific ratios defined for Maca-GO® and Maca-OG™.

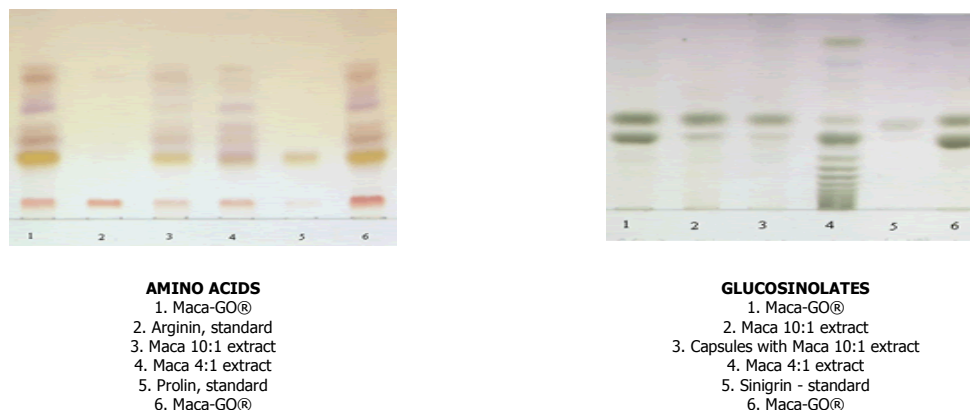


Figure 4: Amino acid and glucosinolate concentrations of different *Lepidium peruvianum* formulations, including Maca-GO®, a 10:1 concentrated product, and a 4:1 concentrated product.

Lepidium peruvianum cultivated for Maca-GO® and Maca-OG™ grows exclusively on land controlled by Natural Health International to ensure that crops grow in their natural habitat, cultivated under strict avoidance of artificial fertilizers and pesticides, and observing 5-year land-rotation practices. Locally employed farmers grow, harvest, select, dry, and process plants in line with traditional farming practices to ensure sustainability, fair trade, ecological viability and cultural integrity in every step of the process.

International, independent, third-party certifying organizations^{16,17} regularly monitor Natural Health International's agricultural and manufacturing practices, and supervise the entire production process to meet or exceed USDA, Japanese, and European Union organic, Kosher, Halal and good manufacturing process (GMP) guidelines.

Preclinical Findings

Preclinical long-term safety testing of a standardized *Lepidium peruvianum* formulation (Maca-GO®) in laboratory animals demonstrated its low toxicity with LD50 values exceeding 15g/kg body weight—well above the 2g/kg body weight limit set by the OECD.¹⁸ No adverse effects were detected in test animals. Histopathological evaluation of their internal organs (liver, spleen, pancreas, testes, and ovaries) after short-term and extended exposure confirmed Maca-GO®'s safety profile.¹⁹ Biochemical and pharmacodynamic studies in rats were indicative of Maca-GO®'s adaptogenic effects on hormones pertaining to the hypothalamic-pituitary-thyroid-adrenal-gonadal endocrine system—including desired, physiological changes in FSH, LH, E₂, P, TSH, T₃, T₄, Cortisol and ACTH—as well as displaying normalizing tendencies on blood cholesterol and triglycerides.²⁰

Clinical Relevance

Traditionally used for its medicinal properties and energizing effects by natives of Peru, *Lepidium peruvianum's* physiological and fertility-enhancing benefits have been reported in publications over the last 20 years.²¹ Apart from symptom relief, of particular importance to menopausal women are *Lepidium peruvianum's* reported effects on sex hormone production, stimulation of body metabolism, increase in energy

and vitality, reduction of excess body weight,^{22,23,24,25} stress control, antidepressant activity, memory improvement, and the enhancement of sexual drive.

Most publications about the use of *Lepidium peruvianum* in menopause, however, only report findings about symptom relief and are mostly based on studies that used non-standardized formulations. Maca-GO® is the first standardized *Lepidium peruvianum* formulation studied in menopausal women for its effect on symptoms as well as on biological markers such as hormone levels, lipids, body mass index and bone density.

Moreover Maca-GO® is the only standardized *Lepidium peruvianum* formulation to demonstrate statistically significant improvements on both symptom relief and hormonal balance. Also, and in contrast to the findings of the Women's Health Initiative (WHI), in which benefits of HRT came along with increases in total cholesterol and triglycerides, Maca-GO® showed a promising trend to lowering total cholesterol in menopausal women. This finding is supported by significant reductions in triglycerides, as well as favorable declines in BMI,²⁶ in addition to significant increases in HDL and significant reductions in LDL.

Multi-center Trial

Results of two pilot studies in menopausal women^{27,15} paved the way for a larger clinical study. Consequently, 168 early post-menopausal Caucasian women were enrolled in a European multi-center clinical study designed to assess biological markers and symptomatic relief from menopausal symptoms to standardized doses of *Lepidium peruvianum* (2g Maca-GO®/day).²⁶

Blood samples were drawn and menopausal symptoms assessed on admission (A) and at the end of every month on either Maca-GO® (M) or placebo (P). Participants were randomly allocated to one of several arms of selected sequences of Maca-GO® (M) or placebo (P) that differed in their length (3 or 4 months).

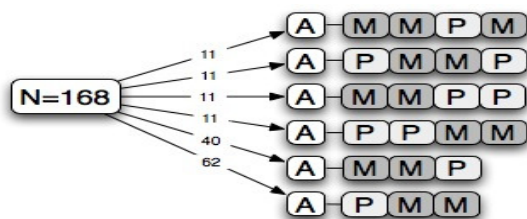


Figure 5: Design of a multi-center study of a standardized *Lepidium peruvianum* formulation (Maca-GO®) in early post-menopausal women (n=168). A=Admission, M=Maca-GO®, P=Placebo.

This approach was chosen to generate a broad set of data with the goal of confirming the outcome of the pilot studies, assess residual effects of Maca-GO® when switching to placebo, and to identify placebo effects in symptom relief as well as changes in biological markers under more expanded, diverse, real-world settings.

Patients were recruited in five urban gynecological clinics in two culturally different cities (Poznan and Glogow, Poland), and randomly assigned to the arms of the protocol under adherence to all relevant ethical and Good Clinical Practice standards.^{28,29}

Blood serum hormone levels (FSH, LH, E₂, P) and lipid profiles (total cholesterol, TG, HDL, LDL) were drawn from pre-assigned patient subsets and measured each month in internationally certified laboratories— together with an assessment of menopausal symptoms according to Greene³⁰ and Kupperman.^{31,32} Data were collected and analyzed with SPSS according to validated statistical tests.

Key Findings

The following is a selection of the most relevant findings representative of *Lepidium peruvianum*'s characteristic effects on hormone levels, lipids, bone density and menopausal symptoms. Each graph shows results from an entry measurement taken at the time of admission (Admission), and then from monthly measurements taken after one month on placebo (Placebo) or on Maca-GO® (Maca).

1. Hormones (Estradiol (E₂), Progesterone, FSH, LH)

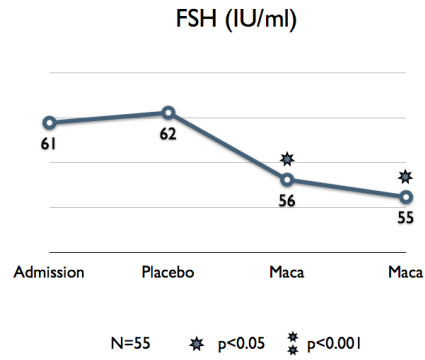
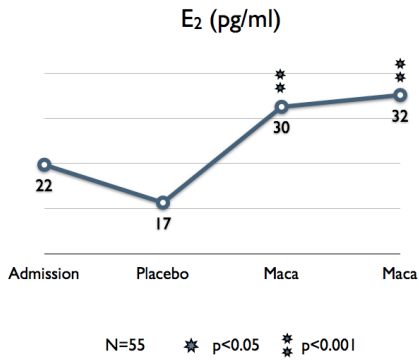


Figure 6: Low initial estrogen levels showed a highly significant increase after one and two months on Maca-GO®.

Figure 7: Initially elevated FSH levels dropped significantly as estrogen production normalized (see Figure 6) after two consecutive months on Maca-GO®.

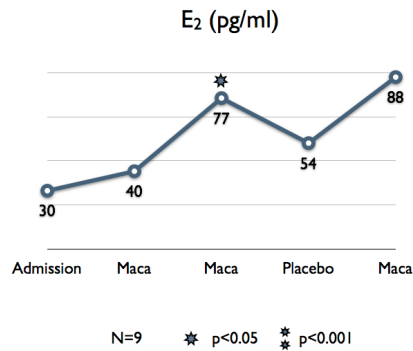
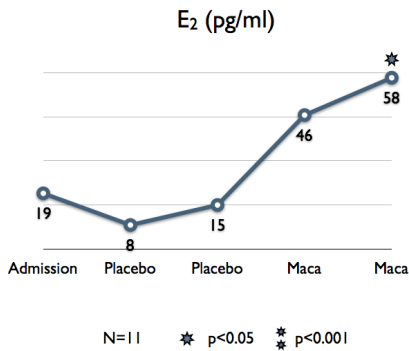


Figure 8: After two months on placebo, two months on Maca-GO® showed significant increases in estradiol.

Figure 9: Maca-GO® for two months, then a month on placebo, and again one month on Maca-GO® showed significant increases in estradiol levels.

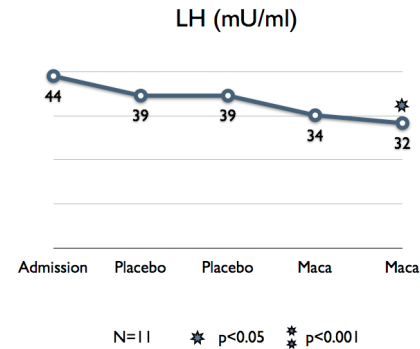
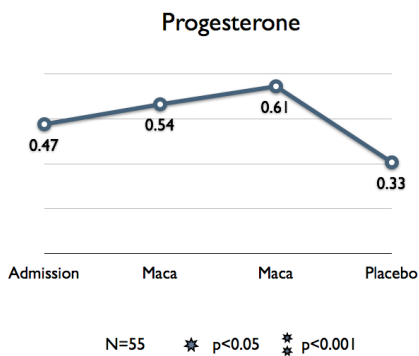


Figure 10: Progesterone level changes were indicative of Maca-GO®'s hormone-balancing effect.

Figure 11: After two months on Maca-GO® a significant decrease in LH was measured.

2. Lipids (HDL, LDL, total cholesterol, TG)

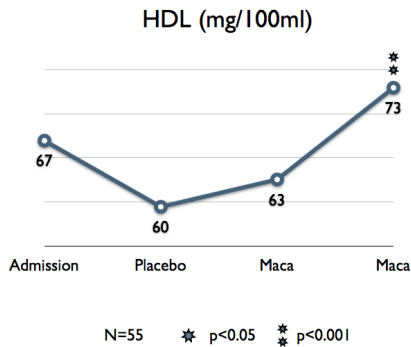


Figure 12: A highly significant rise in HDL was found after two months on Maca-GO®.

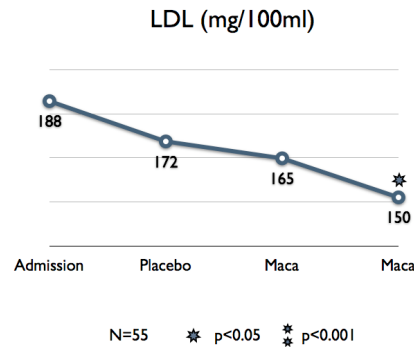


Figure 13: Administration of Maca-GO® for two consecutive months showed a significant reduction of LDL.

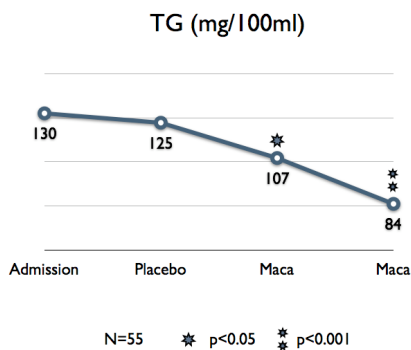


Figure 14: Maca-GO® showed highly significant reductions in triglycerides after two months.

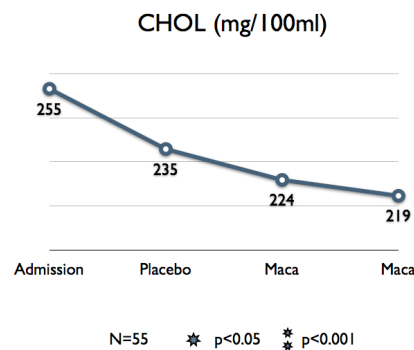


Figure 15: A tendency to lower total cholesterol levels was observed after two consecutive months on Maca-GO®.

3. Bone Density and Menopausal Symptoms

Bone Density (Total Density, Z-Score)

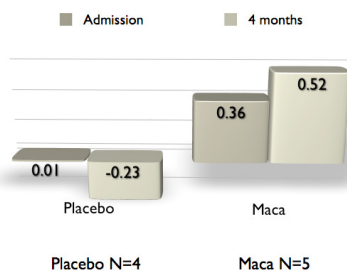


Figure 16: Results obtained on selected cases over four months gave an indication of possible effects of Maca-GO® on bone mass.

Kupperman Index

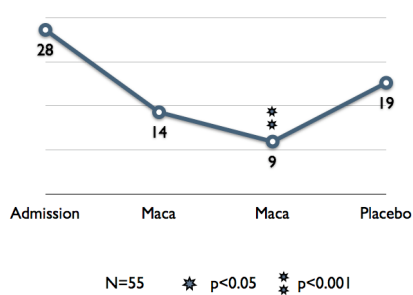


Figure 17: Highly significant reductions of menopausal symptoms according to the Kupperman index after two months Maca-GO®.

Discussion / Conclusion

Maca-GO® does not contain phytoestrogens. Nevertheless, statistically significant changes in hormone levels found in preclinical studies, and also in the first randomized clinical trial performed with *Lepidium peruvianum* (Maca-GO®), were indicative and characteristic of its adaptogenic effects.

Current scientific understanding of adaptogens¹² is based, among other factors, on their influence on key hormones involved along the hypothalamic / pituitary / adrenal / gonadal system. Unlike stimulants, adaptogens don't seem to boost stamina by draining and/or depleting cellular energy reserves; the handful of true adaptogens (a Russian study of 4,000 plants found only 12 in the world)¹² acknowledged as such by reputable, peer-reviewed publications seem to strengthen the body's stress response systems by improving and enhancing nutritional, macromolecular and biochemical cell assets, as well as communication among proteins, cells, the central nervous system and endocrine glands.

The effect of any true adaptogen seems to require a run-in phase of 2-6 weeks during which the organism is induced (next to other physiological enhancements) to adjust key hormone production in relevant endocrine glands. Therefore, statistically significant changes were not consistently found throughout all study arms, and Maca-GO®'s effect was most evident when patients took two consecutive months of Maca-GO®.

The adaptogenic effect of Maca-GO® seems to rely on the particular composition of its constituents—and not on any single chemical entity. Therefore, a high-quality standardized formulation of the entire spectrum of active constituents is critical not only for clinical trials, but especially in real-life settings in which women are subject to specific dietary habits.

Continuous intake of Maca-GO® over 2-3 months showed not only statistically significant results compared to placebo, but also trends indicative of metabolic adjustments that may require more than 2-3 months to come to their full expression, such as levels of total cholesterol and bone density.

Taken together, the presented results form a strong basis for further, more prolonged investigations of the effects of Maca-GO® in menopausal women and also of Maca-OG® in men. The WHI results have precipitated the search for non-hormonal alternatives to HRT that work. Maca-GO®'s profile as a natural, reliably safe, certified organic, standardized and concentrated formulation of *Lepidium peruvianum* seems to be one of the most promising approaches we have to date for both peri and post-menopausal women.

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