Maca

Definition: The *USP–NF* proposed definition for Maca is as follows: Maca consists of the dried hypocotyls of *Lepidium meyenii* Walp. (Fam. Brassicaceae). Other articles derived from Maca include Powdered Maca, which is Maca reduced to a powder or very fine powder, and Powdered Maca Extract, which is prepared from Powdered Maca using suitable solvents such as alcohol and water or a mixture of these solvents.

Other Pharmacopeial Monographs and Regulatory Standards: In Australia and New Zealand, maca is considered *nontraditional* food (rather than *novel* food) and appears in Class 1 Listed medicines.[1] The British MHRA acknowledges the "recorded food use" of maca but states that its "status [is] unclear under food law—advice should be sought from the Food Standards Agency."[2] However, no maca status report was found with the EFSA.[3] Importation of maca into the European Union was initially challenged under the EU Novel Food Regulation 258/97.[4] However, maca currently is classified as "not novel" on the basis of information from the Peruvian tax authority (SUNAT) that reported substantial maca shipments to Italy and Spain.[5]

Chemistry: Air-dried maca hypocotyl is a rich source of carbohydrates (about 59%), but maca also contains protein (10%), moisture (10%), and lipids (2%). Maca has a high concentration of minerals, particularly potassium (2%) and iron (0.016%) in addition to tannins, saponins, amino acids, and sterols.[6,7] Benzylated alkamides frequently referred to as macamides occur in maca at concentrations of 0.0016%–0.0123% in the dried hypocotyls.[8] Maca constituents include fatty acids such as palmitic, oleic, and linoleic acids; sterols such as β-sitosterol, campesterol, and stigmasterol; and aromatic glucosinolates such as glucotropaeolin as well as other benzyl and *p*-methoxybenzyl glucosinolates and their derived isothiocynates.[9,10] Alkamides such as macamides and macaenes may be considered marker compounds for standardization of maca. Total alkamide content varies from 0.15%–0.84%.[11–13] The combination of two glucosinolates, sinigrin and glucotropaeolin, is unique to maca and is considered a chemotaxonomic marker because this combination does not occur in other *Brassicaceae* family members. Maca also contains (1*R*,3*S*)-1-methyltetrahydro-β-carboline-3-carboxylic acid (MCTA).[6,14] The chemistry of maca is reviewed extensively by Valentova et al.[15]

Potential Adulterants and Substitutions: Anecdotal reports suggest that maca powder may be adulterated with yam powder.

Safety Review

Human Data

(A) **Clinical Studies:** A search in the clinical trials registries[CR21–CR27] returned three ongoing studies. Also on record was a completed study that compared a combination of maca and cat's claw with glucosamine taken daily for up to eight weeks. One study group received Reparagen (a combination of a 300 mg cat's claw extract and 1500 mg of RNI 249, an extract of maca) orally twice daily (n = 48), and the comparator group received 1500 mg/day of glucosamine sulfate (n = 47). In this study the tolerability of both treatments was good, and no serious adverse events were noted.[16] Safety reviews by TGA[CR41] and Medsafe[CR46] cited some unpublished clinical studies that reported only nonserious adverse events, specifically mild headache and flushing. In another study Gonzales et al. did not observe any adverse effects in healthy volunteers who were administered 1.5 g/day or 3 g/day for 4 months.[17–20] Dording et al. reported that 3 g/day of maca was well tolerated in a small clinical study (n = 16).[21] In another small randomized placebo-controlled study, maca alone (0.6 g daily) or in combination with silymarin (maca plus silymarin, 0.2 g plus 0.6 g, respectively, daily) was administered for more than 90 days in patients suffering from metabolic syndrome. A moderate increase in aspartate transaminase level and diastolic blood pressure were observed in the maca-only group but not in the silymarin plus maca group.[22] In other studies, maca did not significantly affect serum concentrations of reproductive hormones including testosterone, estradiol, and 17-hydroxyprogesterone in healthy men.[23–25] The Cochrane reviews database returned no reports for the terms *maca* or *Lepidium*.

(B) **Adverse Events:** A PubMed search revealed no case reports of adverse reactions to maca-based products as of July 2009 (search terms: *Lepidium meyenii* AND *maca* AND *adverse* OR *safe* OR *safety*).[CR30] A search in FDA MedWatch returned 22 reports for the period of January 2001 to July 2009.[CR39] All the reports involved multi-ingredient products containing maca as one of the components and typically promoted for enhancement of sexual performance. The reports cited 18 nonserious and four serious reactions. Nonserious reactions included numbness, headache, transient global amnesia, dermatological reactions, seizure, priapism, gastritis, sleep deprivation, bleeding, dizziness, and heart palpitations. Of the four serious reactions, two involved patients who were taking a multi-ingredient weight loss product with an undeclared amount of maca. One patient died, and the other had a stroke and was hospitalized for an extended period of time. The third patient, who had been taking a herbal cleansing product concurrently, had an anaphylactic reaction, was stabilized within three hours, and was discharged from the emergency room. The fourth patient hospitalized for bradycardia had been concurrently taking a multi-ingredient men's vitality performance product for 7–10 days and earlier had undergone heart valve replacement. The Canada Vigilance Program database returned 10 reports for *maca* and *Lepidium meyenii* products.[CR42] The AEs reported included diarrhea, palpitations, sweating, shaking, nausea, abdominal pain, malaise, dizziness, and tachycardia. The British MHRA database included two reports as of September 2009.[CR40] None of these were fatal and included palpitations, convulsion, and urticaria. A search for *maca* or *Lepidium* in EMA[CR20] and EFSA[CR29] did not return any results. The Australian TGA[CR41] yielded five reports for the period from 1960 to July 2009 for maca-containing products (three reports involved for a proprietary product containing 550 mg of maca root per capsule,[26] and two reports were for two different proprietary products containing multiple ingredients in addition to maca. One case reported a mild elevation of liver enzymes (ALT/SGPT) following short-term exposure, but the levels returned to normal within 10 days after dechallenge. Nonserious events reported included: rash, syncope, burning sensation, nausea, abdominal pain, vomiting, diarrhea, dehydration, impaired concentration, headache, epistaxis, anxiety, insomnia, tachycardia, and thirst. The New Zealand Medsafe[CR46] adverse reaction database and the WHO database showed no reports for maca or *Lepidium*.[6]

* References CR1 to CR58 are found at the end of the Introduction

(C) **Usual Recommended Intake:** Maca traditionally is used as food in the Andean high-altitude regions of Peru, Bolivia, and northwest Argentina.[27–29] Chung et al. estimated the consumption at about 50–100 g of dried hypocotyls per day as food.[30] As a dietary supplement the recommended dose range is 1.5–3 g of dried hypocotyls (corresponding to about 10 g of fresh maca).

Experimental Data

(A) **In Vivo Studies:** A dose-response study was performed to determine the safety in rats of orally administered lyophilized aqueous maca extract at 0.01–5 g/kg over seven days.[30] Researchers examined organ weights, stages of the seminiferous tubules, epididymal sperm count and motility, and serum testosterone and estradiol levels. No toxicity was observed in doses up to 5 g of extract/kg. However, the researchers found a significant dose-dependent reduction in seminal vesicles, lowered serum testosterone level, and increased length of stages VII–VIII of the seminiferous tubules. These effects were apparent at 0.01 g extract/kg and showed a maximum effect at 1.0 g/kg. Other parameters such as cauda epididymal sperm count, sperm motility, and serum estradiol level reportedly were not affected at any of the doses studied.[30] In another study Gonzales et al. reported that administration to rats of 66 mg of maca root twice a day for 14 days increased the proportion of germ cells undergoing spermatogenesis in seminiferous tubules.[18] In other studies, Gonzalez et al. postulated that maca's fertility-enhancement activity depended on the strain of mice and maca variety used (e.g., maca varieties include black, red, and yellow).[7,31,32] No adverse effects were observed in any of their studies.

Oshima et al. reported that feeding mice with maca (0.5 g/L) in drinking water for 30 days increased the serum concentrations of progesterone and testosterone but had no effect on the levels of 17β-estradiol or the rate of embryo implantation.[33] Ruiz-Luna et al. observed that treating Balb/c mice with 2 g/kg per day of dry roots of yellow maca for 42 days increased litter size.[34] However, they were unable to explain the increase in uterine weight observed in ovariectomized mice in the treated group. Zheng et al. reported enhanced sexual function in mice and rats administered a 10% ethanol suspension of standardized maca extract orally for 22 days, as measured by an increase in the number of complete intromissions, the number of sperm-positive females, and a decrease in the latency of penile erection in male rats with erectile dysfunction.[23] Chung et al. reported no toxicity in rats administered doses of up to 5 g of lyophilized extract/kg over seven days.[30] A 2010 study showed that supplementation of peripubertal breeding bulls with maca improved sperm quality and motility and had no side effects.[35]

(B) **In Vitro Studies:** In a study that tested the hypothesis that maca contains testosterone-like compounds, various maca organic extracts (in methanol, ethanol, hexane, and chloroform) failed to regulate the glucocorticoid response element activation, thus calling into question its ability to bind the human androgen receptor and promote transcription pathways regulated by steroid hormone signaling.[36] Valentova et al. reported that aqueous and methanolic extracts of maca showed in vitro hepatotoxicity in a rat hepatocyte model and weak estrogenic activity (comparable to the effect of silymarin) in human breast cancer MCF-7 cells. Other researchers reported a weak cytoprotective effect of the extracts in terms of LDH release and AST levels.[37] Maca contains MTCA,[14] which is considered mutagenic in the presence of nitrites[38] but not in their absence.[39] Gonzales and Gonzales-Castaneda did not find maca mutagenic to the *S. typhimurium* TA100 in the absence or presence of S9.[32]

Potential Interactions: Administration of 3 g/day of maca increased sexual function scores in women and men who had developed sexual dysfunction following the use of selective serotonin reuptake inhibitors (SSRIs). Thus, maca may interact with SSRIs such as escitalopram, citalopram, fluoxetine, or paroxetine.[21]

Cautions: Maca has a high concentration of vitamin K, a common constituent in the *Brassicaceae* family, therefore it is possible that the consumption of maca could adversely affect bleeding parameters in patients taking anticoagulant medication (e.g., warfarin). Excess consumption of glucosinolates, coupled with low iodine levels, could precipitate goiter in those with thyroid disorders. The Natural Medicines Comprehensive Database suggests that the use of maca should be avoided during pregnancy and lactation because of the lack of safety information in this special population.[CR33] In a small clinical study, administration of 0.6 g per day maca caused a mild increase in diastolic pressure, and therefore the authors suggested caution in the use of maca in higher doses in hypertensive patients.[22]

No report about maca was found in the Reprotox database,[CR56] and no cautions related to use during pregnancy and lactation were found in all reviewed texts.[CR6,CR9,CR13,CR32,CR35,CR55]

Concluding Remarks: The USP Dietary Supplements Expert Committee (USP-DS EC) noted that maca is traditionally and extensively used in the Middle Andean region (Peru, Bolivia, and northwest Argentina) as a nutritive food, for male and female fertility disorders, and to increase mental and physical energy. Its use has been recorded since 1549.[40] Although maca has a long history of safe use as food, the commercially available dietary supplement dosage forms are not in the form described in traditional practice, which include roasting or cooking in milk or water. The USP-DS EC pointed out that the study by Valentova that suggested that maca might have hypertensive effects is confounded by the patients' metabolic syndrome status. The committee also noted that despite the reported hormonal action in rodents, no hormonal activity has been reported in humans. Considering that 50–100 g per day of maca typically is consumed as food in Middle Andean countries, the use of 1–3 g per day as a dietary supplement is comparatively low. The committee noted that other safety reviews of maca have failed to demonstrate any significant safety concerns. However, it was noted that the use of material not prepared following traditional methods of preparation (e.g., ethanolic extracts) may contain components that would not normally be ingested when maca is eaten raw or prepared following traditional methods. Considering all of the information and further considering that no serious adverse events were found during this review for single-ingredient maca products, the committee voted unanimously to assign the proposed maca articles (Maca, Powdered Maca, and Powdered Maca Extracts) to Class A, thus admitting them for USP monograph development according to the USP *Guideline*.[CR1] *USP General Notices* require that a label for a herb or other botanical such as Maca, Powdered Maca, and Powdered Maca Extracts intended for use as a dietary supplement (and claiming to meet compendial specifications) should bear the statement: "If you are pregnant or nursing a baby, seek the advice of a health professional before using this product."[CR58]

References: (*References CR1 to CR58 are found at the end of the Introduction*)

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