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Review paper

Lepidium meyenii biological activity and future perspectives

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Abstract

Lepidium meyenii Walp. (Brassicaceae) is a plant native to the Andean region. It is also known as Maca and Peruvian ginseng and is considered to have been used in traditional medicine for more than 2000 years. *Lepidium meyenii* is regarded as a plant adaptogen. Nowadays, Maca root is used worldwide as a food, tonic, antioxidant, enhancer of fertility, etc. The main compounds in the underground part of the plant are glucosinolates, thiohydantoins, isothiocyanates, macamides, macaene, fatty acids, polysaccharides, alkaloids, fiber, lipids and proteins, which are responsible for various biological activities including antimicrobial, antioxidant, cytotoxic, anti-inflammatory and immunomodulatory activities. The purpose of this review is to summarize the data of some *in vitro*, *in vivo* and clinical studies on the biological activity of Maca and to analyze the future perspectives for the inclusion of Maca into novel herbal medicines.

Key words: adaptogens, plant adaptogens, Lepidium meyenii, Maca root, macamides, macaene

Introduction

Lepidium meyenii Walp., also known as Peruvian ginseng or Maca (Peres et al., 2020), is a member of the cruciferous family (Brassicaceae), which also includes cabbage, cauliflower, and garden cress (Wang and Zhu, 2019). *Lepidium meyenii* consumption has a rich history in human society and folk medicine. Maca tubers have been consumed since the pre-Inca period and during the Inca period in the Americas, present - day Peru. However, it was mostly used by high society and as a reward for warriors (Piacente et al., 2002). It has been used to treat anxiety, depression and osteoporosis. It has also been used as a fertility and memory enhancer (Tafuri et al., 2021).

Lepidium meyenii is a biennial herbaceous plant reaching 10-20 cm in height. The underground part of the plant is a succulent root divided into two parts. One is known as the hypocotyl and the other is the true root. The hypocotyl is the edible part that lies between the leaves and the root (Bermejo and León, 1994). There are thirteen different phenotypes of hypocotyls depending on its color. According to most studies, 3 of the phenotypes of *Lepidium meyenii* (red, black and yellow) are responsible for its biological activity (Tafuri et al., 2021). The corolla consists of 12-20 leaves and is pinnately divided and rosette-like. The Maca inflorescences are small-flowered. Fruits reach 4-5 mm in length, they are striate, reddish-grey and ovoid in shape. The hypocotyl size is 2-5 cm, and sometimes the entire underground part can reach 20 cm. (Bermejo and León, 1994).

Lepidium meyenii is planted during the rainy season (September - November) alone or together with bitter potato due to the repellent constituents in Maca. The crop is harvested between May and June, but in the first year the hypocotyls have no seeds. Some are placed in a hole and

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covered with a solid cover for 6-7 months. After this period, the seeds (Fig. 1) are already formed (Bermejo and León, 1994).

Fig.1. Seeds of *Lepidium meyenii* Walp

Lepidium meyenii is resistant to strong winds, low temperatures and UV radiation (Wang and Zhu, 2019). Nowadays, the main producer of Maca is Central Peru (Piacente et al., 2002). It is cultivated in the Andean region between 3500-4000 m altitude (Tafuri et al., 2021). *Lepidium meyenii* can also be cultivated in other habitat (Piacente et al., 2002) and is widely planted in Yunnan Province in China (Wang and Zhu, 2019). Countries such as Germany, the Netherlands, Japan, China, Canada, the United Kingdom and the United States are the leading consumers of products of Maca (Wang and Zhu, 2019).

Although the *Lepidium meyenii* root intake has a rich background in the traditional medicine, the number of randomized double-blind clinical trials is limited. However, Maca root and some of its active compounds have great potential to be incorporated into some novel herbal medicines. The purpose of our research is to summarize the data of *in vitro* and *in vivo* studies analyzing the biological activity of *Lepidium meyenii* and to highlight its future possible applications.

Material and methods

The first step of the screening process involved identifying eligible studies. An extensive search of PubMed, Web of Science and Google Scholar databases were performed. The following keywords were used in the search process: **“**adaptogens”, **“**plant adaptogens”, ”Lepidium *meyenii*”, **“***Lepidium meyenii* adaptogen properties study”, **“**randomized controlled study *Lepidium meyenii*”, “Maca root”, **“**Maca”, **“**macamides”, **“**macaene”. In the final stage, relevant studies were selected based on the exclusion and inclusion criteria. The exclusion criteria were: webinars or blogs; articles containing lack of data information. The inclusion criteria were: *in vitro* studies, human studies, animal studies and studies investigating the impact of macaridine and macamide. A total of 43 studies were selected and included in the present review.

Results and discussion

Maca root as an adaptogen

The term “adaptogen” was first introduced by N. V. Lazarev in the middle of the 20th century. The term refers to compounds that have the potential to increase the **“**non-specific” resistance of organisms to adverse effects and stress (EMA, 2008).

Later, the most important pharmacodynamic characteristics of compounds that could be considered as adaptogens were defined. According to Dr. Brekhman, adaptogens must be non-toxic to the recipients and should act by increasing the resistance of the organism to adverse factors (biological, chemical or physical). In 1969, I.I. Brekhman and I.V. Dardymov published the article “New substances of plant origin which increase nonspecific resistance” which discusses the first plants called adaptogens: *Eleutherococcus senticosus* Max., *Aralia manshurica* Rupr. et Max., *Aralia cordata* Thunb., *Aralia schmidtii* Pojark., *Echino panax elatum* Nakai, *Acantopanax sessilifiorum* Rupr. et Max., *Kalopanax septemlobum* (Thunb.) Koidz (Brekhman and Dardymov, 1969). Later, other plant species, including *Lepidium meyenii*, were also regarded as adaptogens. There are also some synthetic molecules that are considered to be adaptogens, some of which (Bromantan) are prohibited by the World Anti-Doping Agency (WADA, 2023).

According to the European Medicinal Agency (EMA), it is important to distinguish the term “adaptogen” from traditional herbal tonics and CNS stimulants of plant origin. For example, many CNS stimulants of plant origin (cocaine, mescaline, cathine, cathinone) have the potential to temporarily enhance the work-capacity. However, this is followed by a period of reduced performance. Moreover, the intake of stimulants is usually characterized by many side effects. In contrast to plant stimulants, plant adaptogens have the potential to increase work capacity that is not followed by a decrease and side effects (EMA, 2008).

In general, adaptogens have significant potential to increase the body resistance. The *Lepidium meyenii* intake is associated with no side or toxic effects (Lim, 2015) and at the same time the plant has a very rich phytochemical composition. Proteins, taurine, BCAA (branched chain amino acids such as valine and isoleucine), Zinc, Mg and Ca are the compounds responsible for its anti-fatigue effect (Lim, 2015). According to López-Fando, *Lepidium meyenii* is able to restore homeostasis (López-Fando et al., 2004). Its intake is also associated with a reduction in symptoms and conditions induced by stress, such as ulcers, elevated glucose levels, increased corticosterone levels, etc. (Lim,

2015). *In vivo* research on mice has showed that Maca extract has the potential to increase physical endurance, increase swimming time, enhanced liver glycogen levels, and reduce lactic acid levels (Choi et al., 2012; Li et al., 2017).

Maca root as functional food

The high nutritional quality of Maca root is based on its composition. It is rich in proteins, vitamins, minerals and carbohydrates. Nowadays, the powdered *Lepidium meyenii* root is a popular functional food used as a nutritious food or energy and fertility booster (Valerio and Gonzales, 2005). Powder Maca root (Fig.2) is used to prepare hot and cold drinks and has a pleasant taste and aroma. The recommended daily use is between 5 and 10 g. A quantity of 100 g powdered *Lepidium meyenii* root provides about 342 kcal; 0.6 g fat; 67 g carbohydrate;10 g fiber and 12 g protein.

Fig. 2. Powdered Maca root.

Hypocotyl is the edible part of the plant and could be consumed dried - in soups, baked foods, cooked foods, as a drink (Piacente et al., 2002). Fresh hypocotyls are harmful, so they are dried naturally in the sun for 4-6 days. They are then moved to dark and cold places where they are stored. Hydration and softening of the hypocotyl is achieved by boiling in water (Valerio and Gonzales, 2005).

Lepidium meyenii hypocotyls can be found as baked goods, beverages, distilled liquors, baking flour, whole maca, and also as nutritional supplements in capsules and pills (Valerio and Gonzales, 2005).

Lepidium meyenii contains ballast substances - dietary fiber. The fiber, more precisely the total dietary fiber, is divided into two groups, soluble and insoluble. Most fruits, vegetables and legumes contain both types of fiber. Insoluble fiber is mostly in the tougher outer layers, while the core is rich in soluble fiber. The two types of fiber complement and help each other. A research has shown that two methods were used to obtain the fiber from Maca liquor residue - enzymatic and chemical. The enzymatic one is superior to the chemical one in terms of functional properties- glucose absorption, oil and water holding capacity. Fibers, especially insoluble ones, retain water and turn into a gel. They are practically not digested by the body and consequently not absorbed by the circulatory system. They enhance satiety and faecal mass, decrease cholesterol levels and influence glycemic response. Fiber can therefore be used in conditions such as diabetes, obesity, asthma and also can reduce the risk of coronary heart disease, hypertension and colon cancer, to prevent hemorrhoids and to reduce the risk of gallstones and kidney stones (Chen et al., 2015).

Biological activity of Lepidium meyenii

The biological activity of *Lepidium meyenii* is due to its hypocotyls. Depending on the hypocotyl color, 13 phenotypes can be distinguished, ranging from white to black. Most studies declare that 3 of the phenotypes of *Lepidium meyenii* (red, black and yellow) are responsible for its biological effects on the human body (Tafuri et al., 2021). The less utilized parts of the plant are the leaves, stem and inflorescence (Wang and Zhu, 2019). The height of the plant is about 10-20 cm, but sometimes the root size can reach 20 cm. Morphologically, they differ in weight (1-5 kg) and shape (spindle-shaped, spherical oval, oval, spherical) (Wang and Zhu, 2019).

The chemical composition of hypocotyl can be divided into primary metabolites, which are responsible for its nutritional value, and secondary metabolites. The primary metabolites are proteins, fibers, lipids, carbohydrates, free fatty acids such as: oleic, linoleic, palmitic, amino acids such as glutamic acid, arginine, aspartic acid, leucine, isoleucine, lysine, phenylalanine, alanine, valine, serine. Also, threonine, tyrosine, histidine, proline, hydroxyproline and methionine. The minerals contained in *Lepidium meyenii* root are calcium, zinc, iron, copper, potassium (Valerio and Gonzales, 2005). Leucine, isoleucine, lysine, phenylalanine, valine, threonine, methionine are essential amino acids and their deficiency can lead to low immunity, digestive problems, stunted growth and development in children.

Secondary metabolites in Maca hypocotyls are maca alkaloids, macamides, macaridine and glucosinolates. They are responsible for the biological activity of the plant (Tafuri et al., 2021) - immunomodulatory activity, antioxidant activity and influence of sexual disorders (Li et al., 2017).

The structure of glucosinolates includes a sulfonate group, a thio-β-D-glucopyranoside chain, and a side chain (R group). Depending on the side chain, they are divided into aromatic glucosinolates, aliphatic glucosinolates, and indole glucosinolates (Yan et al., 2022). *Lepidium meyenii* has nine different glucosinolates, such as *p*-hydroxybenzyl glucosinolate (GSB), *m*-methoxybenzyl glucosinolate (GLH), benzyl glucosinolate (GTL), but their percenteage contents are different in leaves and roots (Yan et al., 2022).

Glucosinolates are hydrolyzed by the enzyme myrosinase after damage to plant tissue to products such as isothiocyanates (ITCs), thiocyanates, nitriles, epithionitriles, oxazolidine-2-thiones, which have effects

on inflammation and cancer (Yan et al., 2022).

The chemical composition of the root varies depending on cultivation site, harvest time, environmental conditions, soil type and phenotype. Recent research has shown the difference between cultivated *Lepidium meyenii* in Peru and China. Seven cultivars were used in the study, six from China and one from Peru. The one cultivated in Peru showed lower levels of dietary fibers (soluble and insoluble) and proteins compared to those cultivated in China. However, the levels of lipids, total alkaloids and minerals were almost equal in most of the cultivars. Compared to Chinese cultivars, the *Lepidium meyenii* cultivated in Peru had lower levels of N-benzyl hexadecanamide and benzyl glucosinolate (Carvalho et al., 2020).

These results lead to the conclusion that the composition as well as the biological effects of the Maca root depend on the seeding and cultivation area, but the color of the root also affects them. In summary, many *in vivo* and *in vitro* studies have been conducted to investigate the positive properties and effects of *Lepidium meyenii*. Different parts of the plant have been examined, but its hypocotyl has been prioritized. The hypocotyls of the different phenotypes have a slight difference in composition, but this does not lead to significant variation in their effect. The high nutritional quality is based on its composition as the desired effects are due to the secondary metabolites - alkaloids, macamides, macaridine and glucosinolates (Tafuri et al., 2021). Glucosinolates are metabolized to isothiocyanates (ITCs), thiocyanates, nitriles, etc., which affect inflammation and cancer (Yan et al., 2022).

Lepidium meyenii is used as food, dietary supplement, antidepressant, energizer, anti-fatigue agent. Also, a neuroprotectant, antioxidant and fertility enhancer as it reduces ROS (reactive oxygen species) as well as triglyceride and transaminase levels, proving its hepatoprotective activity. Hypocotyls are effective on viral cells but have no antibacterial and antifungal activity. Maca root positively affects glucose levels, improves bone density. Management of neuropathic and joint pain is based on the macamides and glucosinolates in the root composition. It is mostly used to improve sexual function as it affects sperm quality, sperm motility and reduces the latent period of erection (Ai et al., 2014; Brooks et al., 2008; del Valle Mendoza et al., 2014; Gonzales et al., 2010, 2013; Gonzales-Arimborgo et al., 2016; Greco et al., 2021; Melnikovova et al., 2015; Pino-Figueroa et al., 2011, 2010; Tenci et al., 2017; Zhang et al., 2017; Zheng et al., 2000; Zhou et al., 2022; Zhu et al., 2021).

In vitro studies for *Lepidium meyenii* have mainly focused on investigating the anti-inflammatory, neuroprotective and antioxidant potential of *Lepidium meyenii* extracts (table 1).

Table 1. Biological activity of *Lepidium meyenii* - in vitro studies

Study Objectives	Study Design	Main results	Ref.
Lepidium meyenii, hypocotyls powder	*In vitro* investigation of essential oils, lipids and polysaccharides from Black, Red and Yellow Maca.	The effect of Black Maca was higher than that of the other phenotypes, but all showed antioxidant activity.	(Sun et al., 2018)
Lepidium meyenii, hypocotyls	*In vitro* investigation of the anti-inflammatory effect of *Lepidium meyenii* on intestinal cells.	The *Lepidium meyenii* polysaccharides affected the level of interleukins, which proves their anti-inflammatory effect on the intestine.	(Chen et al., 2022)
Lepidium meyenii, leaves (aqueous extract)	*In vitro* analysis of the antioxidant effects of polysaccharides from *Lepidium meyenii* leaves.	Polysaccharides from *Lepidium meyenii* leaves neutralized hydroxyl radicals and DPPH (2,2-diphenyl-1-picrylhydrazyl) radicals, demonstrating a dose-dependent antioxidant effect.	(Caicai et al., 2018)

Lepidium meyenii (methanolic extract)	*In vitro* investigation of the effect of *Lepidium meyenii* on influenza A and B viruses.	*Lepidium meyenii* extract affected viral cells by slowing or stopping their growth.	(del Valle Mendoza et al., 2014)
Lepidium meyenii, Black, Red or Yellow Maca (hydroalcoholic extracts)	*In vitro* investigation of the effect of *Lepidium meyenii* on bones in mice with surgically removed ovaries over a period of 4 weeks.	Red and Black Maca improved bone density.	(Gonzales et al., 2010)
Lepidium meyenii (ethanolic extract and powder)	*In vitro* study of *Lepidium meyenii* ethanolic extract and powder and their effect on *E. coli*, *Ps. Aeruginosa*, *St. aureus*, *Candida*, etc.	No significant effect was observed on destruction of microorganisms.	(Mohammadbeigi et al., 2019)
Lepidium meyenii, (Choline chloride/1,6-hexanediol in ratio 1:2 with20% water)	*In vitro* research on the effect of *Lepidium meyenii* on damaged PC12 cell line.	The neuroprotective effect of *Lepidium meyenii* is based on the macamides in the composition.	(Li et al., 2023)
Lepidium meyenii, (powder, dimethyl sulfoxide)	*In vitro* research of the effect of *Lepidium meyenii* extract on initially frozen and defrosted bull semen for 24h.	*Lepidium meyenii* extract positively affected DNA to the greatest extent, which is of major importance in the freezing and defrosting process.	(Leiva-Revilla et al., 2022)
Lepidium sativum, seeds (*n*-hexane extract)	*In vitro* study of the effect of *Lepidium sativum* on two types of hepatocellular carcinoma cell lines(HEPG-2 and HuH-7).	As a result, a significant reduction in gene expression was observed in these two lines and this enables *Lepidium sativum* to be used for the treatment of hepatocellular carcinoma.	(Nazir et al., 2021)
Lepidium peruvianum, (ethanolic extract)	*In vitro* study of the effect of *Lepidium peruvianum* and its glucosinolate metabolites as acetylcholinesterase (AchE) and butyrylcholinesterase (BuChE) inhibitors.	The study by molecular docking proved the inhibitory activity of Maca on AchE and BuChE. Maca could be used to slow the progression of neurodegenerative diseases.	(Tarabasz et al., 2022)

Lepidium sativum, (methanolic extract)	*In vitro* study of the effect of *Lepidium sativum*, Commiphora molmol and albendazole on trichinellosis, caused by nematode.	After a 24-hour incubation, larvae and worms were not alive with all three preparations tested, but Commiphora molmol was recommended as an additional treatment to albendazole.	(Abuelenain et al., 2022)
Lepidium meyenii, (powder, dimethyl sulfoxide)	*In vitro* study of the effect of *Lepidium meyenii* on sperm from transgenic mice and human sperm by sperm motility analysis system.	*Lepidium meyenii* enhanced sperm motility and acrosome reaction, which ameliorate fertilization.	(Aoki et al., 2018)
Lepidium sativum, seeds (aqueous - methanolic extract)	*In vitro* examine of the spasmodic effect of *Lepidium sativum* on tissues, isolated from rabbit, mouse and guinea pig.	The results showed that *Lepidium sativum* could be used for constipation and indigestion.	(Najeeb-Ur-Rehman et al., 2011)

Lepidium meyenii extracts did not show *in vitro* antibacterial activity. In 2014, *del Valle Mendoza* reported activity against influenza A and B viruses (del Valle Mendoza et al., 2014). Recently, there has been a great demand for medicines with potential for prevention of viral infections. However, more studies are needed to confirm the potential of *Lepidium meyeni* in influenza prevention or treatment.

Overall, *in vitro* studies have shown promising results in the field of neuroprotection, which is based on the macamides in the composition of the plant. Antioxidant activity has also been observed. Inhibition of AchE could be used to delay the development of neurodegenerative diseases.

Table 2 summarizes the data on the biological activity of *Lepidium meyenii* obtained from animal studies.

Nowadays, there is a great demand for potential medicines that can provide memory enhancement and neuroprotection, and *Lepidium meyenii* could be a promising source for the development of novel medicines in this field.

Data from animal studies confirmed most of the results obtained from *in vitro* research. For example, neuroprotection was also confirmed *in vivo.* However, this also needs to be confirmed in double-blind randomized trials. Furthermore, it would be particularly useful to investigate the effects not of the whole extract but of specific molecules found in *Lepidium meyenii,* which are responsible for this biological activity.

Although *Lepidium meyenii* is used as fertility enhancer in the traditional medicine, studies with humans have not confirmed an improvement in sperm morphology, motility and volume. However, sperm concentration has been found to be ameliorated (Alcalde and Rabasa, 2020) and the quality of sperm has been significantly improved (Melnikovova et al., 2015). Overall, more studies are needed in this area. The intake of *Lepidium meyenii* by individuals with reproductive problems could be an interesting area for future research.

It would also be important to analyze the molecules in the extract that are responsible for the improvement of sperm quality.

The data on the biological activity studies of *Lepidium meyenii* in humans are summarized in Table 3.

Lepidium meyenii has been found to provide a positive effect on depression. Moreover, it has been reported that the intake of *Lepidium meyenii* shows dose-dependent improving effect on sexual dysfunction caused by SSRIs (Selective Serotonin Reuptake Inhibitors). It would also be especially interesting to investigate the potential synergism of *Lepidium meyenii,* its active secondary metabolites and the SSRIs.

Table 2. Studies on *Lepidium meyenii* Walp.

Study Objectives	Study Design	Main results	References
Lepidium meyenii Walp. (aqueous extract)	*In vitro* and *in vivo* investigation of the muscle anti-fatigue activity of *Lepidium meyenii* aqueous extract based on accumulation of metabolites and reactive oxygen species (ROS).	*Lepidium meyenii* aqueous extract reduced the accumulation of metabolites and ROS in skeletal muscle cells and played a significant role in the regulation of exercise-induced fatigue in mice.	(Zhu et al., 2021)
Lepitium meyenii (pentane extract)	*In vitro* and *in vivo* investigation of the action of *Lepidium meyenii* pentane extract as a neuroprotector in crayfish.	An important relashionship was observed between the neuroprotective effect and the concentration of *Lepidium meyenii* in crayfish.	(Pino-Figueroa et al., 2010), (Pino-Figueroa et al., 2011)
Lepidium meyenii, (aqueous extract)	*In vivo* and *in vitro* research on a mouse, injected with D-galactose, and SH-SY5Y cells, damaged with H_2O_2.	The research showed that *Lepidium meyenii* reduced the level of LDH (Lactate dehydrogenase). Maca has an antioxidant and neuroprotective activity.	(Zhou et al., 2022)
Lepidium meyenii, (aqueous extract)	*In vitro* study on Hep-G2 cells, damaged with alcohol. *In vivo* study on mice with alcoholic liver disease.	The main polysaccharide in *Lepidium meyenii* decreased the levels of triglycerides and transaminases (hepatoprotective activity).	(Zhang et al., 2017)
Lepidium meyenii, Black Maca (aqueous extract)	*In vivo* study of the effect of *Lepidium meyenii* on the ability to learn on mice with surgically removed ovaries, 7 days after the procedure. Water Morrise maze and step-down test were used. *In vitro* research on the brains to define MAO (monoamine oxidase), Ache (acetylcholinesterase), MDA (methylene dioxyamphetamine).	The aqueous Black Maca extract reduced the activity of Ache and MDA. MAO was not affected. Black Maca has the potential to improve memory.	(Rubio et al., 2011b)

Lepidium meyenii, Walp. (aqueous extract or acetonitrile/methanol-1:1)	*In vitro and in vivo* examine of the effect of *Lepidium meyenii* on chronic pain.	Reduction of the neuropathic and joint pain in rats.	(Tenci et al., 2017)
Lepidium meyenii, (dried powder)	*In vivo* research on *Lepidium meyenii* as a functional food in Oncorhynchus mykiss (Walbaum).	The results showed development in size, health and orientation in Oncorhynchus mykiss (Walbaum).	(Lee et al., 2004)
Peruvian maca (dried powder)	*In vivo* examine of sperm increasment in horses with 20g/day of *Lepidium meyenii* powder for 60 days.	The root maca powder improved the concentration of the sperm and its quality in horses.	(Peres et al., 2020)
Lepidium meyenii	*In vivo* examination of the effect of *Lepidium meyenii* on sperm concentration in mice (controlled group and used THC (tetrahydrocannabinol), Maca, or combination of THC/Maca).	The quality of the sperm was better in the controlled and THC/ Maca groups rather that the THC and Maca groups.	(Greco et al., 2021)
Lepidium meyenii (lipid extract)	*In vivo* investigation of the effect of *Lepidium meyenii* oral pure lipid extract on erectile dysfunction in rats.	The pure *Lepidium meyenii* lipid extract reduced the latent period of erection and improved the sexual function.	(Zheng et al., 2000)
Lepidium meyenii, Red Maca (aqueous extract)	*In vivo* examine of reducing the size of ventral prostate in normal and medicated with testosterone enanthate rats.	The aqueous extract of Red Maca reduced the epithelial height , ventral prostate weight and affected duct luminal area. The extract also had effects on estradiol and testosterone levels.	(Gonzales et al., 2005)
Lepidium meyenii Walp. (aqueous extract)	*In vivo* investigation of the immunomodulatory activity of *Lepidium meyenii* on cyclophosphamide injected mice.	The immunomodulatory activity of *Lepidium meyenii* is based on its polysaccharides which inhibited the apoptosis of lymphocytes and affected positive the Th1/Th2 balance.	(Fei et al., 2022)

Lepidium meyenii (dried extract, spray)	Red Maca spray extract was used on male mice with damaged skin tissue for 7 days straight.	Improvement of the healing process of the wound in mice, living at high sea level.	(Nuñez et al., 2017)
Lepidium meyenii, Yellow Maca cream (lyophilized aqueous extract)	*In vivo* investigation of skin UV irritation and damage on mice.	Photoprotective effects.	(Castañeda-Alarcón et al., 2021),
Peruvian Maca, Black Maca (hydroalcoholic extract)	*In vivo* research on the effect of Black Maca and mixture of Black Maca/Yacon on mice with induced diabetic with streptozotocin for 7 days.	The Black Maca itself or in combination with Yacon affected positively the glycemic levels.	(Gonzales et al., 2013) (Gonzales et al., 2013)
Lepidium meyenii (aqueous extract)	*In vivo* study of *Lepidium meyenii* toxicity on nematode *Caenorhabditis elegans* reproduction caused by enhanced apoptosis process.	The *Lepidium meyenii* alkaloids are responsible for the enhanced apoptosis process in germ cells.	(Pilissão et al., 2023)
Lepidium meyenii, Black Maca (hydroalcoholic extract)	*In vivo* study (Water Morris maze) on the effect of *Lepidium meyenii* extract on the memory and orientation of mice given oral ethanol for 28 days.	The Black Maca hydroalcoholic extract contains polyphenols, which positively affected the ethanol-induced disorientation.	(Rubio et al., 2011b)
Lepidium meyenii (petroleum ether extract)	*In vivo* study of *Lepidium meyenii* extract as an antidepressant in mice for 6 weeks.	The *Lepidium meyenii* petroleum ether extract enhanced the dopamine and norepinephrine, decreased the ROS levels, serotonin was not affected. Therefore, *Lepidium meyenii* extract has the potential to be used as an antidepressant.	(Ai et al., 2014)(Ai et al., 2014) (Ai et al., 2014)

Future potential for the use of Lepidium meyenii

The neuroprotective activity of *Lepidium meyenii is* attributed to the macamides. The macamides (N-benzylhexadecamide, N-benzy-(9Z,12Z)-octadecadienamide, N-(3-methoxybenzyl)-hexadecanamide, etc.) are secondary metabolites in the composition of Maca and are responsible for its biological activity as a neuroprotectant (Zhu et al., 2020). Although the plant and some of its compounds (macamides) have the potential to be included in some new herbal medicines, studies on humans are limited. However, *in vitro* and animal studies have shown some promising results double-

blind randomized human studies would be particularly useful for better understanding the real potential of *Lepidium meyenii*. For example, the neuroprotective activity of Maca is associated with the macamides (N-benzylhexadecamide, N-benzy-(9Z,12Z)-octadecadienamide, N-(3-methoxybenzyl)-hexadecanamide, etc.) (Zhu et al., 2020). These compounds could be explored in future researches associated with neurodegenerative diseases such as Alzheimer's with dementia and Parkinson's.

Alzheimer's disease occurs with reduced levels of acetylcholine in the synaptic cleft due to increased activity of the enzyme that breaks it down, acetylcholinesterase (AChE) (Patel et al., 2018). *Lepidium meyenii*, Black Maca, inhibits AChE and improves memory. This has been demonstrated by many studies, one of which is related to aqueous extract of Black Maca and its effects on mice with surgically removed ovaries (Rubio et al., 2011a).

It does not cure the disease as well as synthetic medications, but can slow its progression. Therefore, additional research is needed.

Parkinson's disease (PD) is a neurological disorder characterized by loss of dopaminergic neurons in the substantia nigra, leading to basal ganglia dysfunction. The most obvious symptoms are tremor, bradykinesia and muscle rigidity. The development of depression or dementia is often observed in patients with Parkinson's disease. Like Alzheimer's disease, Parkinson's disease is incurable, but with the appropriate medications, its progression could be delayed (Banjari et al., 2018). *Lepidium meyenii* as a herbal remedy contains many important constituents such as amino acids, which are primary metabolites. Some of the amino acids are valine, tyrosine, arginine, tryptophan as a serotoninergic substance, phenylalanine with antidepressant activity, etc. Also included in the composition of the root are sterols, vitamins such as vitamin C and vitamin B3, minerals. Vitamin C has hypotensive, hypocholesterolemic, anti-inflammatory and antineuralgetic effects. Niacin (vitamin B3) has antineuralgic and serotoninergic activity (Banjari et al., 2018). A study was done with *Lepidium meyenii* extract and its effect on PC12 cells exposed to the toxic action of 6-hydroxydopamine. Methanolic extract of *Lepidium meyenii* leaves showed antioxidant effect. This is relevant to Parkinson's disease, as oxidative stress worsens the symptoms of the disease (Rodríguez-Huamán et al., 2017). Many *in vitro, in vivo* and clinical investigations are needed to prove the effects of *Lepidium meyenii* on neurodegenerative diseases.

In Latin America *Lepidium meyenii* is used as an antihypertensive remedy. A study was conducted that proved the activity of Maca as an ACE inhibitor and compared the action of methanolic extract of Maca with Quinapril (Ibrahim et al., 2022), (Ranilla et al., 2010).

Many *in vitro* studies proved the effect of *Lepidium meyenii* as an anti-fatigue agent. One of these studies showed that *Lepidium meyenii* intake in mice prolonged their swimming time, increased their energy and strength. A recent clinical study in athletes proved that intake of Black Maca over a period of time, reduced inflammation, increased physical endurance and body weight (Lee et al., 2023). Also, many *in vitro* tests as well as clinical studies are needed to prove the influence of *Lepidium meyenii* on glucose metabolism. One of the studies used diabetic mice as well as healthy mice divided into 5 groups - healthy, diabetic and treated with Purple, Yellow and Black Maca. All extracts of *Lepidium meyenii* administrated orally decreased and restored glucose to normal levels. Black Maca had the greatest effect on lipid oxidation. Yellow Maca reduced protein carbonyl levels. Purple Maca enhanced the activity of antioxidant enzymes in the liver and blood cells. Also, only Purple Maca alone resulted in an increase in the level of glutathione, which is an antioxidant (Peres et al., 2020; Qiu et al., 2016).

Another study used Black Maca dried spray on diabetic mice - 2g/kg for 14 days. After a few days, the glycaemic level in the mice taking *Lepidium meyenii* was significantly lowered compared to those not taking it (Peres et al., 2020; Troya-Santos et al., 2017). *Lepidium meyenii* could also be studied in humans with reproductive problems. According to Peres, it has the potential to improve semen quality (Peres et al., 2020). A study was conducted with Yellow Maca and its effect on sperm in breeding horses. In recent years, only the semen has been used and transported, not the horses themselves, but for this to happen, the semen is refrigerated. As a result, sperm motility is lowered and sperm quality is impaired by reactive oxygen species (ROS), which are normally neutralized in the testicles with enzymatic and non-enzymatic antioxidant systems. The use of dietary supplements that reduce oxidative stress can improve lipid composition and membrane stability during storage. Several studies have shown that *Lepidium meyenii* improves the quality and concentration of the sperm, based on fatty acids (primary metabolites) and macamides (secondary metabolites) in the composition. They affect oxidative stress and act directly on the reproductive tract. The study was carried out with Yellow Maca hypocotyls and examined its effect on 10 stallions in good health and equally turned out. *Lepidium meyenii* has preserved semen motility, improved semen production and positively affected the semen quantity in raw and subsequently chilled semen (Del Prete et al., 2018).

Lepidium meyenii is a plant with a great potential to influence a variety of symptoms, conditions, and diseases. Although it has been used in the past, more clinical double-blind, randomized trials are needed to prove the current and future potential of Maca.

Conclusion

The underground part of *Lepidium meyenii* is edible and has been known for its advantages and properties since

the 13th century at the time of Incas. In modern times, Maca continues to be studied and used as a dietary supplement. Many *in vitro* and *in vivo* studies have demonstrated the biological activities due to the diversity in the chemical composition of *Lepidium meyenii.* Also, the composition of the hypocotyls is influenced by the place of cultivation, environmental conditions and its color, with different phenotypes occurring. Three of them (Red, Black and Yellow) are responsible for its biological effects on the human body. The leaves are less common but can also be used. *Lepidium meyenii* is used as a food, dietary supplement, antidepressant, energize and anti-fatigue agent, for treatment of anxiety, memory, osteoporosis, as neuroprotector and hepatoprotector. Furthermore, it affects glucose levels, improves bone density and sexual function.

Table 3. Lepidium meyenii studies

Study Objectives	Study Design	Main results	References
Lepidium meyenii Walp. (powder)	Double-blind study, analysing the effect of *Lepidium meyenii* on men fertility. 20 men were included in the research for 12 weeks.	Compared to placebo the quality of sperm was significantly improved.	(Melnikovova et al., 2015)
Lepidium meyenii, Black and Red Maca (dried extract, spray)	Examination of the desired and undesired consequences of using *Lepidium meyenii*. The study includes 175 people, living on sea level and above sea level, receiving 3g Maca (Black,Red) and placebo for 12 weeks.	The Black Maca and Red Maca extracts affected positively blood pressure, fertility, depression, anxiety, energy, glycemia with slight discrepancies due to their different phenotype.	(Gonzales-Arimborgo et al., 2016)
Lepidium meyenii, (powder, into gelatin capsules)	Double-blind, compared with placebo, randomized research of the effect of *Lepidium meyenii* in conditions as asthenozoospermia and oligozoospermia. 69 patients were involved for 12 weeks.	No significant effect was observed on sperm morphology, motility and volume. The sperm concentration was ameliorated.	(Alcalde and Rabasa, 2020)
Lepidium meyenii, (gelatinized Maca in tablets)	Double-blind, randomized study of the effect of Maca Gelatinizada on libido. 57 men, for 12 weeks.	*Lepidium meyenii* did not affect the serum testosterone but improved sexual desire.	(Gonzales et al., 2002)
Lepidium meyenii, Yellow Maca (gelatinized Maca in capsules)	Double-blind study, analysing effect of *Lepidium meyenii* on infertility. 50 men, for 16 weeks.	No hormonal changes were observed.	(Melnikovova et al., 2021)

Lepidium meyenii, (powder in capsules)	Double-blind, randomized study of the effect of *Lepidium meyenii* for improving libido, which is decreased by a selective-serotonin reuptake inhibitors (SSRI). 17 women were included, for 12 weeks.	The *Lepidium meyenii* showed dose-dependent improving effect on sexual dysfunction caused by SSRI.	(Dording et al., 2008)
Lepidium meyenii, (powder in capsules)	Double-blind, compared with placebo, randomized examine of the effect of *Lepidium meyenii* on depressions and blood pressure in 29 postmenopausal Chinese women for 12 weeks.	The *Lepidium meyenii* did not affect the hormonal levels but decreased the blood pressure and had a positive effect on the depression.	(Stojanovska et al., 2015)
Lepidium meyenii, (powder in tablets)	Randomized, compared with placebo examine of the effect of Maca and Yacon, combined with silymarin. 95 patients, for 90 days.	The combination Maca/silymarin decreased the diastolic blood pressure.	(Valentová et al., 2008)
Lepidium meyenii, (powder in tablets)	Double-blind, compared with placebo, randomized research of the effect of *Lepidium meyenii* on mild erectile dysfunction. 50 men, 12 weeks.	An improvement in sexual dysfunction has been observed with the use of *Lepidium meyenii*.	(Zenico et al., 2009)
Lepidium sativum (powdered dried seeds)	A study of the effect of *Lepidium sativum*, alendronate or combination of them on postmenopausal osteoporotic 45 women with chronic periodontitis. For 6 weeks and combined therapy for 6 months.	*Lepidium sativum* itself or in combination with alendronate prevented bone loss on postmenopausal women.	(El Kilani et al., 2019)
Lepidium meyenii, (powder)	A research on the efficacy of *Lepidium meyenii* in female sexual dysfunction. 14 women were included, receiving 3.5g/day of Maca for 6 weeks.	*Lepidium meyenii* could be used as an alternative to affect female sexual dysfunction.	(Mazaro-Costa et al., 2010)(Brooks et al., 2008)
Lepidium meyenii, (capsules)	Double-blind, randomized study. 95 participants, 8 weeks.	Improvement of pain and rigidity in osteoarthritis patients.	(Mehta et al., 2007)

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Резиме

Биолошка активност и идни перспективи на Lepidium meyenii

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Клучни зборови: адаптогени, растителни адаптогени, Lepidium meyenii, корен од мака, макамиди, макаен

Lepidium meyenii Walp. (Brassicaceae) е растение што потекнува од регионот на Андите. Познато е и како Мака и перуански женшен и се смета дека се користи во традиционалната медицина повеќе од 2000 години. Lepidium meyenii се смета за растителен адаптоген. Во денешно време, коренот од Мака се користи во светот како храна, тоник, антиоксиданс, засилувач на плодноста итн. Главни соединенија во подземниот дел на растението се глукозинолати, тиохидантоини, изотиоцијанати, макамиди, макаен, масни киселини, полисахариди, алкалоиди, влакна. липиди и протеини, кои се одговорни за различни биолошки активности како што се: антимикробно, антиоксидативно, цитотоксично, антиинфламаторно и имуномодулаторно. Целта на овој преглед е да ги сумира податоците од некои ин витро, ин виво и клинички студии за биолошката активност на растението Мака и да ги анализира идните перспективи за вклучување на ова растение во составот на новите хербални лекови.