In infertility, erectile Dysfunction, oligozoospermia,

R_x

Fertrogen PRO™

HORNY GOAT WEED EXTRACT 500 MG WITH MACA ROOT EXTRACT 75 MG

To Treat

erectile dysfunction
premature ejaculation
infertility

FertilMed
ANDROLOGY
CREATE LIFE WITH SCIENCE

FertilMed
ANDROLOGY

PRODUCT MONOGRAPH

Fertrogen™ PRO

FertilMed Think Positive...

ANDROLOGY

Fertillmed Pharma is a young and dynamic pharmaceutical company that was established in 2021 in Bangalore, India. Our company is fully integrated and specializes in developing and manufacturing products that address male sexual health issues. We believe in delivering high-quality products to our customers, and we achieve this by partnering with world-standard Quality manufacturers who have global approvals such as cGMP guidelines as laid down by leading regulatory authorities such as USFDA, MHRA - UK, SAHPRA-SOUTH AFRICA, TGA - AUSTRALIA, ANVISA BRAZIL, WHO - GENEVA, TPD - HEALTH CANADA, PPB - KENYA, NDA UGANDA, MOH - SUDAN, INVIMA - COLOMBIA, TFDA TANZANIA, ZIMBABWE, BFARM-GERMANY & OTHER AFRICA, ASIAN & CIS COUNTRIES. This ensures that our products are manufactured in facilities that meet international quality standards and have undergone rigorous testing and inspections.

Bioactive components vare chemical compounds found in natural sources such as plants, fungi, or animals that have biological activity and can have potential health benefits. These components are extracted from natural sources (PHENOLICS, ALKALOIDS, TANNINS, SAPONINS, LIGNIN, GLYCOSIDES, TERPENOIDS) using various methods, including solvent extraction, steam distillation, and enzymatic extraction. Once extracted, the bioactive components undergo purification and are used as ingredients in pharmaceutical products. Using bioactive components from natural extractions has several advantages. First, these components are often well-tolerated by the body and have a lower risk of side effects compared to synthetic chemicals by using bioactive components from natural extractions,

Fertillmed Pharma can develop innovative and sustainable products that address the needs of its customers. These products are safe, effective, and have the potential to improve the quality of life

"BREAKTHROUGH ADVANCEMENTS IN SEXUAL HEALTH

FERTOGEN PRO

YOUR TRUSTED ALLY IN COMBATING ERECTILE DYSFUNCTION, PREMATURE EJACULATION, AND INFERTILITY"

Fertrogen PRO™

PREFACE

We are excited to introduce Fertrogen Pro, a breakthrough solution for the treatment of erectile dysfunction, premature ejaculation, and infertility. As medical professionals, we understand the challenges you face when addressing these complex and sensitive issues among your patients. That's why we have developed Fertrogen Pro, a unique formulation that combines the potent benefits of Horny Goat Weed Extract and Maca Root Extract to provide comprehensive support for sexual health.

Fertrogen Pro combines Horny Goat Weed Extract at a concentration of 500 mg and Maca Root Extract at 75 mg. Horny Goat Weed Extract, also known as Epimedium, has long been recognized for its effectiveness in improving erectile function. It works by inhibiting the enzyme phosphodiesterase type 5 (PDE5), which helps promote increased blood flow to the penile area, resulting in stronger and longer-lasting erections.

Maca Root Extract, derived from the Peruvian Maca plant, has a rich history of use in traditional medicine for its aphrodisiac and fertility-enhancing properties. It supports sexual function by promoting hormonal balance and improving sperm production and motility, making it a valuable addition for patients experiencing premature ejaculation and infertility.

When combined, Horny Goat Weed Extract and Maca Root Extract in Fertrogen Pro create a powerful synergy, addressing multiple aspects of sexual health. By inhibiting PDE5, Fertrogen Pro helps improve erectile function, while the fertility-enhancing properties of Maca Root Extract support the overall reproductive health of your patients.

Together, let us harness the potential of this unique combination to empower your patients to overcome these challenges and restore their sexual health and well-being. Experience the transformative benefits of Fertrogen Pro and make a lasting difference in the lives of your patients.

OVERVIEW OF ERECTILE DYSFUNCTION IN INDIA

Erectile dysfunction (ED) is a prevalent condition affecting a significant number of men in India. It is characterized by the consistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance. ED not only impacts a man's physical health but also his emotional well-being and intimate relationships.

In India, the prevalence of erectile dysfunction has been steadily increasing over the years, with factors such as lifestyle changes, stress, sedentary habits, and chronic diseases contributing to its rise. Additionally, cultural and social factors can often lead to hesitation or embarrassment among men when seeking professional help for their sexual health concerns.

Fortunately, awareness and understanding of erectile dysfunction have been growing in India, and healthcare professionals are playing a crucial role in addressing this issue. With advancements in medical science, there are effective treatment options available that can significantly improve the quality of life for men living with ED.

Treatment approaches for erectile dysfunction in India typically include lifestyle modifications, such as regular exercise, maintaining a healthy diet, managing stress levels, and avoiding smoking or excessive alcohol consumption. Additionally, medical interventions may involve the use of oral medications, such as phosphodiesterase type 5 (PDE5) inhibitors, which help enhance erectile function by increasing blood flow to the penis.

In more complex cases or when medications are not suitable, healthcare providers may recommend alternative therapies like vacuum erection devices, penile injections, or surgical options. Psychological counseling and couples therapy can also play a vital role in addressing the emotional aspects associated with ED.

It is important for men in India to understand that erectile dysfunction is a treatable condition, and seeking professional help is essential for proper diagnosis and personalized treatment plans. Healthcare providers across the country are well-equipped to provide the necessary support and guidance to help men regain their sexual confidence and improve their overall well-being.

By fostering open conversations and raising awareness about erectile dysfunction, India is making significant strides in ensuring that men have access to the resources and support they need to address this common issue. Together, healthcare professionals, patients, and society can work towards breaking the stigma surrounding ED and promoting a healthier and more fulfilling sexual life for men in India.

ERECTILE DYSFUNCTION IS SOON GOING TO BE AN EPIDEMIC AMONG THE YOUNGER GENERATION

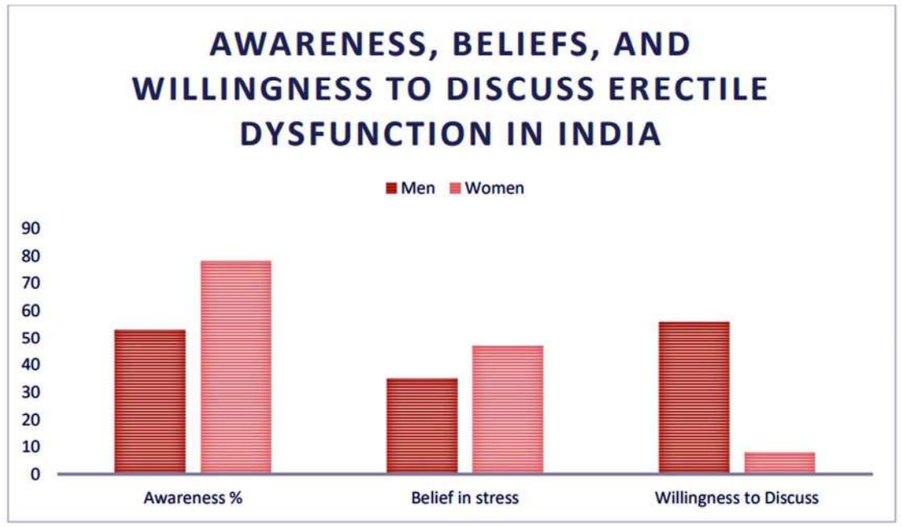
SEXUAL HEALTH EXPERTS

Fertrogen PRO™

ERECTILE DYSFUNCTION IN INDIA

20% of Men across all the age groups and 30% of men younger than 40 battle ED[1,2]

75% of Men 66% Women think ED is not an old age Problem



Only 53% of men are unaware while 78% of women in India are aware of ED. Out of this 35% of men and 47% of women believe that stress is the major catalyst.

As far as actually discussing this concern with their partners is concerned, only 56% of men and 10% of women are willing to do so.

Even though treatment is readily and easily available, men often shy away from addressing this condition, which can lead to relationship and health problems.

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SEXUAL INTIMACY IS KEY TO COUPLES TODAY

28%
OF WOMEN

"MIGHT CONSIDER SEPERATION IF THIER PARTNER DOES NOT TAKE CORRECTIVE ACTIONS FOR ED"

Fertrogen PRO™

96%

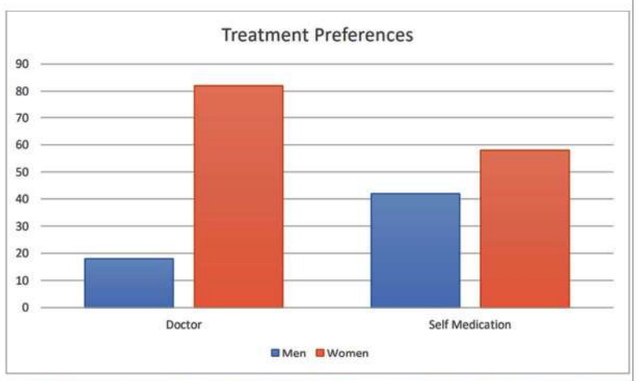
DOCTORS

agreed that partners play a significant role in the success or failure of the man's ED treatment and may influence decisions regarding treatment and even its continuation.

82% of women believe that consulting a doctor is better than self-medicating.

42% of men prefer self Medication preferred by known Chemist

61% of men would consult a doctor and get treated by the medication prescribed by the doctor



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TREATMENT

FIRST LINE THERAPY

ORAL MEDICATIONS

1. PHOSPHODIESTERASE INHIBITORS

SILDENAFIL - Relaxes muscles found in the walls of blood vessels and increases blood flow to particular areas of the body. Sildenafil is used to treat erectile dysfunction in men.

TADALAFIL - PDE5 inhibitor marketed in pill form for treating erectile dysfunction.

VARDENAFIL - Used to treat erectile dysfunction in men. It works by increasing blood flow to the penis during sexual stimulation. This increased blood flow can cause an erection.

Apomorphine-Dopamine agonist

2. TOPICAL PHARMACOTHERAPY

Several vasoactive drugs (2% Nitroglycerin, 15-20% Papaverine gel. and 2% Minoxidil solution or gel) have been used for topical application to the penis

3. VACUUM CONSTRICTION DEVICE

Common adverse events of the three PDE5* inhibitors

Adverse Event	Sildenafil (0%)	Tadalafil (0%)	Vardenafil (0%)
Headache	12.80	14.50	16
Flushing	10.40	4.10	12
Dyspepsia	4.60	12.30	4
Nasal Congestion	1.10	4.30	10
Dizziness	1.20	2.30	2
Abnormal Vision	1.90	-	<2
Back Pain	-	6.50	-
Myalgia	-	5.70	-

*PDE5 - Phosphodiesterase type 5

RISK FACTORS

Concomitant (e.g.. within 24 hrs for Sildenafil and Vardenafil, and 48 hrs for Tadalafil) use of nitrate-containing medications (e.g.. Nitroglycerin, Isosorbide dinitrate) is an absolute contra-indication to PDE5Is use, as it can cause severe hypotension that can result in death.

PDE5Is for patients who have recent serious cardiac events, poorly controlled hypertension, unstable angina or retinitis pigmentosa should be used with caution.

SECOND LINE THERAPY

INTRACAVERNOUS INJECTION with single or combination vaso-active agents (commonly Alprostadil, Papaverine, Phentolamine, & Moxisylyte) was once the most frequently used therapies for ED before the PDE5Is' era.

TRANSURETHRAL MEDICATION

Alprostadil used in intracavernous injection can be applied transure thrally at a higher dose (250-1000 µg) as a therapy for ED with a success rate of 40-69%.

TESTOSTERONE REPLACEMENT THERAPY

PENILE PROSTHESIS

SEX THERAPY

NATURAL PRODUCTS

Fertrogen PRO™

Fertrogen PRO™

HORNY GOAT WEED EXTRACT 500 MG
MACAROOT EXTRACT 75 MG

Fertrogen PRO™

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BIOCHEMISTRY
HORNYGOAT WEED EXTRACT

COMPOSITION

Horny Goat Weed is a common name for the plant genus of Epimedium from the family Berberidaceae. When sold as a supplement, they are standardized for their Icariin content, which is seen as the active ingredient.

The genus of Epimedium contain (specific plants in brackets):

- Icariin, the prenylated diglycosdie flavonoid known as the active ingredient[1]
- Structurally similar compound to Icariin, the Epimedium compounds A, B and C[1]
- Quercetin[1]
- Ikarioside A and B (wanshanense)[1]
- Anhydroicaritin and Desmethylanhydroicaritin (wanshanense) [1]
- Sagittatoside B (wanshanense)[1]
- Diphylloside A and B (wanshanense) [1]

STRUCTURE

Icariin is known as a 'prenylated diglycoside of kaempferol'. Specifically, the basic structure has a prenyl-group attached to the kaempferol molecule (depicted below, its the bendy tail heading upwards from the hexagon) and has two sugar molecules attached to it; a glucose molecule at R2 and a rhamnose molecule at R1. The other three popular molecules found in Horny Goat Weed, Epimedin A-C, have the same following backbone but just different sugars at R1 and R2.

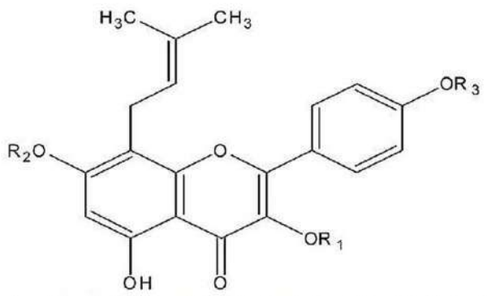

Image from: (Chen Y, et al. Intestinal absorption mechanisms of prenylated flavonoids present in the heat-processed Epimedium koreanum Nakai (Yin Yanghuo). Pharm Res. (2008))

Icariin has a molecular weight of 676.67g/mol.[2]

Similar compounds would be the compound Icaritin, which has -OH groups where both sugars would be (R1, R2) and Desmethylicaritin which has -OH groups at all R positions. Both of these compounds are found co-existing in the Horny Goat Weed plant.[3,1]

PHARMACOLOGY

1.Intestinal absorption

Icariin is not a stable compound in the human intestine due to enzymes present. Icariin, along with three other compounds native to the parent plant of Horny Goat Weed (Epimedin A, B and C), as prenylated flavonoids, are rapidly digested into their respective metabolites in the intestinal environment via hydrolysis. These four compounds seem to mostly have their rhamnose sugar cleaved off during this process.[4] Co-ingestion of a lactase phlorizin hydrolase (Lactase) inhibitor increased the absorption of the active ingredients, preserving 40-62% of the original Icariin content.[5] Without said lactase inhibitor, bioavailability of straight Icariin is approximately 12%.[6]

Icariin metabolizes to Baohuoside I, which is the same structure but with one less glucose moiety. The loss of the glucose moiety can more than double transit into the intestinal membrane.[7] The absorption of baohuoside (and other related compounds) is outranked by the fast efflux back into the lumen, an active transport mediated by MRP2 and BCRP (Breast Cancer Resistance Protein); inhibiting MRP2 may increase absorption of baohuoside I.[7] These receptors may possibly be overridden, as increasing the concentration of baohuoside I decreases the efflux efficiency.[7] When in the intestines, Baohuoside I does not appear to be further metabolizes, due to an apparent lack of appropriate intestinal glycosidases (in rats and vitro).[7]

Efflux of Icariin from the intestinal wall into the lumen occurs via P-glycoprotein efflux pumps.[7]

2.Colonic

Icariin, if not absorbed, can be sent to the colon and transformed via bacteria into Icariside II, a potentially more erectogenic compound than Icariin.[9]

POSSESSES ACTIVE INGREDIENT THAT EXERTS APHRODISIAC PROPERTIES.

3.SYSTEMIC

After intravenous administration in rats, Icariin at 10mg/kg bodyweight had a half-/-life of 0.562+/-0.2 hours and an elimination rate constant (Ke) of 1.361+;0.556 per 1/h.[10] Another study using Icariin at the same dose via injection, however, noted a half-life of 170+/-75.1 minutes suggesting quite a bit of variability (Ye et al. 1999).[11]

After oral ingestion of 4.5mg/kg Icariin in rats, a Cmax of 3.37+/-1.42mg/L, an AUC of 40.6+/-5.73mg/h/L with a half-life of 10.9+/-1.35 hours is seen. Elimination rate constant is 0.064+/-0.1 per 1/h.[12]

A study on Horny Goat Weed dosed at 1.64g/kg (4.38mg/kg Icariin) orally showed a Cmax of 2.41+/-0.2mcg/mL, an AUC of 23.62+/-1.37mcg/h/mL, a Tmax of 1.55+/-0.53 hours and a half-life of 0.11+/-0.07 hours.[6] This study also compared Horny Goat Weed ingestion against a combination of HGW and two other herbs (Nepal dock root and Ficus hirta yahl; three main ingredients of a chinese medicine) and found that the Cmax of Icariin was higher (3.13+/-0.29µg/ml) as was the AUC (30.84+/-3.68mcg/h/mL) the half-life (0.35+/-0.32 hours) and the Tmax was prolonged (2.06+/-0.15 hours) when coingested.[6] It is not known what compound in the 8 herb mixture bettered the pharmacokinetic profile of Icariin.

Another chinese mixture of herbs featuring Horny Goat Weed (Er-Xian) at 4.8g/kg orally, measured parameters (Cmax, AUC, Half life and Elimination Constant)do not reach the level of 4.5mg/kg Icariin, yet Icariin's absorption appears to have been increased as Horny Goat Weed only comprised 19% of the mixture by weight and the results were quite comparable.[12]

4.EXCRETION

The major metabolic pathway of Icariin appears to be biliary excretion, or ejecting the Icariin with bile salts into the intestinal lumen to leave in the feces.[13] Coingestion of P-Glycoprotein inhibitors can reduce the elimination of Icariin,[13] possibly by the aforementioned inhibition of intestinal efflux.[7][14]

INCREASES NITRIC OXIDE SYNTHESIS AND INHIBITS PDE5 IN CAVERNOSAL SMOOTH MUSCLES.

EXERTS POSITIVE NEUROTROPHIC EFFECT ON NITRERGIC NERVES,ENHANCES SMOOTH MUSCLE PROLIFERATION & MIMICS ENDOGENOUS ANDROGENS.

5.INTERACTIONS WITH NEUROLOGY

KINETICS

Icariin is able to cross the blood-brain barrier[15] and after intravenous injection, Icariin and the three diglycoside compounds (Epimedium A-C) are found in the brain, although mostly Epimedium C. Icariin appeared to be more localized to the sciatic nerve.[16] A study using Icariin liposomes intravenously found about 1.83% of the injected dose to be found in the brain after injection of 20mg/kg Icariin liposomes and neural levels exceeded 0.2mcg/g brain mass.[11]

NEUROPROTECTION

Icariin also has the ability to act as a neuroprotectant via inhibiting pro-oxidant and pro-inflammatory markers in response to stress[17][18] and can attenuate cognitive decline induced by D-galactose injections at a dose of 60mg/kg bodyweight (injection).[19] In vitro studies suggest it can also protect neurons from damage induced by Lipopolysaccharide (a pro-inflammatory agent)[20][21] and theoretically against aging as assessed by a senescence accelerated rat model.[22] High dose oral Icariin (75-150mg/kg bodyweight) was associated with improved cognitive biomarkers such as superoxide dismutase and glutathione in these rats.[22]

In one study it was shown to exert protective effects via SIRT1 expression and subsequent PCG-1a expression.[23]

HORNYGOAT WEED EXTRACT INTERACTIONS WITH HORMONES

TESTOSTERONE

Supplementing with oral Icariin at 1-5mg/kg BW in castrated rats showed significant differences in erectile potency but minimal changes in testosterone. Specifically, 1mg/kg bodyweight restored testosterone to baseline after penile injury while 5,10mg/kg bodyweight was ineffective.[33] Null results were found in rats with removed testicles, with absolutely no changes in testosterone at 1 and 10mg/kg bodyweight Icariin.[34]

One study using 200mg/kg (of a lower purity, 40%; bioequivalent to 80mg/kg) Icariin over 7 days noted that, in a chemically castrated group (average testosterone level of 0.78+/-0.44ng/mL) was able to increase testosterone to almost triple (10.93+/-2.03ng/mL) the control group (3.01+/-0.41ng/mL).[2] LH and FSH did not differ between groups, and the mechanism of action was hypothesized to be in the testes as previous studies on rats without testes showed absolutely no changes in serum testosterone,[34] although the difference in dosage is also a possibility, as one study was conducted on cavernous crushing noted some difference at 1mg/kg bodyweight, and higher doses were insignificantly suppressive relative to control.[34]

The above oral dose of 80mg/kg pure Icariin, after conversions to humans based on Body Surface Area,[35] appears to be 12.8mg/kg bodyweight Icariin or 1163mg Icariin daily for a 200lb human.

SEEMS TO HAVEA THE MECHANISMS TO INCREASE TESTOSTERONE

INCREASES SEXUAL DESIRE AND ACTIVITY WHEN COMPARED TO SILDENAFIL.

ERECTION

Icariin is a selective PDE5 (enzyme) inhibitor[36] with an IC50 value between 0.75-1.1mM depending on PDE5 isoform[36] and an EC50 of about 4.62mmol/L in increasing cGMP in the corpus cavernosum of the penis;[37] Icariin has approximately 100-fold greater affinity for PDE5 than other PDE isozymes.[38] This effect can be potentiated by the modification of two hydroxyethyl ether moieties to the compound, which increase this inhibition 80-fold,[39] but this modification is not naturally occurring. At 10mg/kg bodyweight in mice (110mg for a 150lb human) Icariin exerts pro-erectile properties[34] and seems to have more effectiveness following repeated doses.[33][34] It has shown efficacy over 30 days at 5-10mg/kg in an animal model of erectile dysfunction related to blood flow,[40] which correlates to a 55-110mg dose for a 150lb man.

Other compounds in the Epimedium family that have PDE5 inhibitory potential are Icarisid II derived from Epimedium wanshanense (not significantly different in potency than Icariin; approximately half of Viagra)[41]

Lower doses (1-5mg/kg) are able to improve neuronal Nitric Oxide Synthase (NOS) expression[34] and inducible (iNOS) expression[33][34] content in addition to PDE5 inhibtion. Effects on iNOS and nNOS do not appear to differ greatly from each other at the dosages of 1mg, 5mg, and 10mg/kg bodyweight,[34] suggesting low doses could also exert benefit but by different means.

ICARIIN MAY ALSO PROMOTE NITRIC OXIDE SIGNALLING VIA INCREASING EXPRESSION OF NOS ENZYMES, WHICH MAY WORK SYNERGISTICALLY WITH THE PDE5 INHIBITION

Icariin has also been linked to increasing neurite growth of major pelvic ganglia in vitro[34] which may be downstream of P13K and MEK/ERK activation.[42]

BENEFICIAL EFFECTS ON NEURONS MAY EXTEND TO THE PELVIS

SAFETY AND TOXICITY

No designated toxicology studies have been conducted on Icariin, although the highest dosage used in rats currently is 200mg/kg bodyweight Icariin for 7 days which showed no signs of clinical toxicity.

Case Studies

One case study has been published in which a 66-year old man suffered from hypomania (persistently euphoric and irritated mood) and Tachyarrhythmia (abnormal rhythm of the heart and increased heart rate) associated with Horny Goat Weed.[44] The side-effects occurred after 2 weeks of supplementation (undisclosed brand and dose), and coingested pharmaceuticals included beta-blockers, statins, aspirin and viagra. Subject had bipolar disorder not otherwise specified prior to the onset of results.[44]

Another case study noted benign rashes develop after ingestion or Horny Goat Weed and Ginkgo Biloba; both were taken at the same time, so its not sure which contributed or whether the combination is at fault.[45] Subject was an otherwise healthy 77 year old man taking the compounds orally.

Erectile Dysfunction

Retrograde Ejaculation

Hypogonadism (Low Testerone)

DNA Damage In Sperm

Fertrogen PRO™

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BIOCHEMISTRY
MACA ROOT EXTRACT

COMPOSITION

'Maca' is the common word to refer to the plant Lepidium Meyenii, of the genus Lepimedium and the famile of Brassicaceae; this family is that which also holds cruciferous vegetables such as broccoli, cauliflower, collard greens, and mustard. The plants most closely related to Maca (taxonomically) are rapeseed, mustard, turnip, black mustard, cabbage, garden cress, and water cress.[1] Maca has been traditionally used as a folk medicine for vitality and fertility in the Andean region of Peru and has been used in both genders as well as animals,[1][2] and is sometimes referred to as Peruvian Ginseng despite not bearing any resemblance to the Panax Ginseng plant of its family.[1] It is grown exclusively in the Andean Region of Peru at a height level of 4000-4500m above sea level[3] as its growing conditions require winds, cold, and ample sunlight[1] and possibly being more conducive to growth, as one study noted growth rates were faster with lower temperatures.[4] Interestingly it appears Maca may reverse the decrease in spermatogenesis that occurs at this height range (in rats).[5]
When used as a food product, the bulbous hypocotyls (stem-like protuberances) are dried and then eaten to levels upwards of 20g daily with no reported side-effects associated with this method, and when dried hypocotyls can be stored for years.[1] Maca is frequently boiled and drunk as a juice, due to the storage form of dried hypocotyls being too hard to bite. Modern usage of maca tends to be capsules.

Nutritionally, Dried Maca is:[1][3]

10.4% water content unless otherwise dehydrated[3]

10.2-16% protein by weight, with a small sarcosine content (0.70mg/100g)

59% carbohydrate

2.2% lipid (of which 40.1% are saturated and 52.7% unsaturated)

8.5% fibers

Minerals are calcium (150mg/100g), copper (5.9mg/100g), zinc (3.8mg/100g), and potassium (2050mg/100g) and the overall Ash content is 4.6%[3]

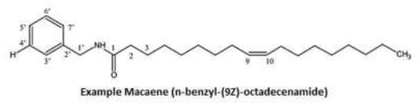
Vitamins such as Vitamin C (8mg/100g), Riboflavin (650mcg/100g), and Thiamine (280mcg/100g)[3]

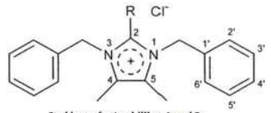
Phenolic compounds (at around 5.5-7.6mg/g, poor content)[6]

53 Essential Oils (aromas) with most being Phenyl acetonitrile at 85.9%[7]

The noncaloric bioactives found in Maca tend to be:
Macaridine[12] and Maca alkaloids that are exclusive to Maca[1]
Macaenes which are Maca-exclusive unsaturated fatty acids[13][14] and include
Macamides, which are amine derivatives of the Macaenes;[15] some include n-benzylhexadecanamide and n-benzyloctadecanamide[15] and range from 0.0016 to 0.0123% dry weight (low content)[15]
Lepidine A and B,[16] two imidazole alkaloids with the names 1,3-dibenzyl-4,5-dimethylimidazolium chloride and 1,3-dibenzyl-2,4,5-trimethylimidazolium chloride; respectively
Glucosinolates such as glucoalyssin (0.6-0.9% total glucosinolates[9]), glucosinalbin (0.02-0.028% total glucosinolates[9]), glucobrassicanapin, glucobrassicin, glucoaubrietin (aka. glucolimnathin; 6-6.2% total glucosinolates), 4-methoxyglucobrassicin, glucotropaeolin (80-90% total glucosinolates[17][9]),[9][1] and Benzyl glucosinolate (7.01-17.5mg/100g dry weight of Red Maca)[18] with aromatic glucosinolates consisting of up to 99% of total glucosinolates by weight with no significant differences between ecotypes.[17][9]
7 alkamides[14]
Methyltetrahydro-β-Carboline molecules such as MTCA[19] in the butanolic fraction[20]
Beta-Sitosterol[12]


Macaridine


Example Macaene (n-benzyl-(9Z)-octadecenamide)


Backbone for Lepidiline A and B
(Hydrogen and Methoxy; respectively)

The alkaloid known as macaridine is said to be the main bioactive, as well as some glucosinolate content; the macaene fatty acids are unique to Maca, but their content as well as the amount of their derivatives in Maca (the macamides) may be too low to be the main bioactives

Interactions with Hormones

Testesterone

1.5g and 3g of Maca for 12 weeks failed to increase circulating testosterone levels in healthy men.[40] These same doses have been used in a 12 week study by other authors in men, and it was noted an increase in aphrodisia (as assessed by self-report) that reached 24.4%, 40%, and 42.2% of the subjects in Maca at 4, 8, and 12 weeks (respectively) while placebo had no increase at weeks 8 and 12; this increase in aphrodisia was independent of testoterone, which did not differ between groups.[22] No androgenic effects or increases in testosterone are seen in postmenopausal women taking 3.5g Maca daily for 6 weeks.[31]

Maca does not appear to have significant androgenic interactions beyond circulating testosterone, as this study failed to note any interactions of Maca components with the androgen receptor.[41]

Luteinizing Hormone

A 12 week study in healthy men taking either 1.5g or 3g of Maca daily failed to significantly influence circulating luteinizing hormone levels at 4, 8, or 12 weeks in time.[40] A lack of effect has also been observed following 3.5g daily ingestion for 6 weeks in post-menopausal women.[31]

Safety and Toxicology

General

No significant toxicity has been reported in human consumption with Maca root, with one study reporting that 0.6g Maca for 90 days was associated with an increased serum ALT and diastolic blood pressure.[37] and rats have tolerated up to 5g/kg bodyweight without adverse effects.[58] In human trials of up to 3g of Maca a day is well-tolerated, and the traditional method of boiling up to 20g of Maca to make into juice has not currently been associated with much toxicity.[59]

Pregnancy

Currently, the only evidence investigating a link between Maca consumption and Pregnancy is one conducted in mice where 1g/kg lyophilized (2.16g/kg dry weight) Maca, correlating to traditional usage amounts and consumed prior to and shortly after fertilization, noted increased litter size without any influence on gender ratios and not associated with any adverse pup morphology or viability.[60] This was independent of any increases in implantation rates, the fertility index, or pup survival; all of which were similar between groups. No human evidence on safety nor adverse reports appear to exist.

Testicles

In a study on lead-induced testicular damage where rats were fed lead for 35 days and Maca was introduced on day 18, it was demonstrated that 2.2g/kg Maca daily (boiled hypocotyl extract) acted to attenuate the reduction in seminal vesicle weight that occurred from lead exposure while preserving the weight of the testicle.[42]

In regards to spermatogenesis, it has been reported that Black Maca has more beneficial effects on spermatogenesis relative to Yellow and Red[43] as the increase in daily sperm production seen with Yellow and Red sometimes fails to reach statistical significance.[10] A comparative study between different extracts of Black Maca over 7 days noted that the ethyl acetate fraction was the most effective fraction for increasing daily sperm production although the chloroform extract appeared to be the one that increased sperm count in the vas deferans while both were equally effective in increasing sperm count in the epididymus.[53] In general, improvements in daily sperm production can be seen from day 1 of supplementation in rats[43] and improvements in sperm count can be seen independent of increased daily sperm production.[54] These increases in daily sperm production appear to be related to increasing the onset of spermatogenesis.[55][56][57]

Maca is also able to reverse suppression of spermatogenesis and sperm count induced by lead even when lead exposure precedes and continues through Maca administration[42] and has been associated with preserving the reduction in spermatogenesis induced by high elevation.[5] Interestingly, this conclusion could be an explanation as to why Maca has such an impressive history of fertility usage as it is grown exclusively in heights of 4000-4500m above sea level while this study was conducted at 4340m.[3]

Phytochemical and biological assessments on *Lipidium meyenii* (maca) and *Epimidium sagittatum* (horny goat weed)

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Abstract: The effects of *Lipidium meyenii* (maca, LM) and *Epimidium sagittatum* (horny goat weed, ES) have been investigated due to their involvement in fertilization. Both of the drugs showed good results before, during and after fertilization in male and female mice. The results revealed that the crude extract of *Lipidium meyenii* caused a significant decrease in the no. of writhes at 300 and 500mg/kg ($p<0.05$) as compare to control, *Epimidium sagittatum* and standard drug. The gross behavioral, open field, exploratory behaviour, forced swimming test for stress, diuretic activity, chronic toxicity with the effect on reproduction of both male and female and change in body weight were also studied. The phytochemical study showed the presence of tannin, alkaloid, carbohydrate, rich protein and absence of sterol in LM, whereas ES shows presence of sterol and less protein. LS improve in muscle activity and exploratory behaviours without any toxic effects on mice and their pups. It does not have diuretic effect for first two hour but act normally after initial phase of drug therapy. *Epimidium sagittatum* has dual action that is at low dose it has slight stimulation action and at high dose little depressive effect. ES also has some diuretic effect. Overall these results suggest that LM is highly effective remedy for treatment of impotency and reduces stress and depression, because of dual effect ES not only suggested as an anxiolytic medicine but also effective in female hormonal disorder.

Keywords: *Lipidium meyenii*, *Lipidium meyenii*, diuretic, infertility.

INTRODUCTION

Recent advancement in the field of drug evaluation have made it necessary to modify the traditional views or rather explore them based on the current results carried out using the modern scientific methods used for pharmacognostical and pharmacological investigations. The two selected herbal ingredients namely *Epimedium sagittatum* (Horny Goat Weed) and *Lepidium meyenii* (Maca) have been in use by the mankind since decades but the recent developments has uncovered many of their hidden benefits along with their safety profiles. However, because of their great potential in the field of herbal drugs there still exists a room to conduct more research on them to verify the claimed benefits & investigate their margin of safety in particular and moreover, to expand the research beyond their traditional major uses so that the mankind gets maximum of their benefits. Both the ingredients have got aphrodisiac properties & widely used as food supplements alone or in combination with other food supplements.

The research shows that 70% of mental illnesses occur with stress. This gives us a pessimistic view of involvement of stress in reproductive disorder. This thought help to up bring the knowledge of those medicines having potential to use in erectile dysfunction, impotency, infertility associated with psychological disturbances.

There are a huge range of such kind of remedies to the public, practitioners and established health clinics. These remedies can provide many benefits for a variety of situations, but patient compliance decreases due to their side effects, for example the intraurethral therapy causes complications such as pain or uneasiness in the penis, surrounding areas (testicles, legs and perineal), some time hot or burning feeling appears in urethra and swelling of legs (Raina *et al.*, 2001). Therefore this study might be helpful for to solve this problem in a better ways.

Lipidium meyenii (Maca) herbal remedy and uses as a energy food. Most commonly it is used for fertility enhancement and aphrodisiac qualities due to its energizing effects. Traditionally it is used to promote mental clarity, in impotency, menstrual irregularities in female, menopause and chronic fatigue syndrome (Brooks *et al.*, 2008). The roots of *L. meyenii* are relaxant, nutritive, aphrodisiac and immunity enhancer (Brooks *et al.*, 2008).

The whole plant of *Epimidium sagittatum* is

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antirheumatic, aphrodisiac, carminative, expectorant, ophthalmic and vasodilator. Used as a kidney tonic, it also treats sterility and barrenness (Bown 1995). It is taken internally in the treatment of asthma, bronchitis, cold or numb extremities, arthritis, lumbago, impotence, involuntary and premature ejaculation, high blood pressure and absentmindedness (Bown. 1995). It should be used with some caution since in excess it can cause vomiting, dizziness, thirst and nosebleeds (Bown 1995). The plant is harvested in the growing season and dried for later use (Bown1995).

MATERIALS AND METHODS

Preparation of extracts

The plant materials were collected at Karachi, Pakistan. The plants were identified and voucher specimen No. LM/ES/0306 were deposited in the herbarium of Research Institute of Pharmaceutical Sciences, Department of Pharmacognosy, University of Karachi, Karachi, Pakistan. The fresh plant materials were chopped into small pieces. The chopped material was macerated with ethanol for 15 days (2 times) at room temperature. The ethanol extract was then filtered and evaporated under reduced pressure in rotary evaporator to yield a residue.

Animals and drugs

The following drugs were used: Diazepam and acetylsalicylic acid (Merck) and Furosimide, Imipramine. Swiss albino mice male and female (25-30) were used. They were housed under a 12h light and dark cycle at 22 ± 2°C with *ad libitum* access to food and water. Animals were acclimatized at the laboratory for at least 1 h before testing. All animals were fasted over night before test, water was supplied. Plant drugs and standard drug were dissolve in distilled water immediately prior to use and plant drugs given orally according to body weight. Control animals received the same dose of vehicle under the same conditions.

Phytochemical analysis

The preliminary phytochemical tests on plant drugs were done by qualitative analysis standard methods (Trease and Evans, 1983; Plummer, 1985; Wallis, 1985).

Assessment of analgesic activity

By writhing method

These tests were performed according to the modified method of Koster *et al.,* 1959 and Turner 1965. Mice were used as the test animals in this method. According to this method writhes were induced by intraperitonial administration of the acetic acid solution 10ml/kg. Thirty minutes prior to the administration of the acetic acid, the animals were treated orally with the test substance. Numbers of writhes was counted for 30 minutes immediately after acetic acid administration. A reduction in the number of writhing as compared to the control animals was considered as evidence for the presence of analgesia and expressed as percent inhibition of writhing.

Mice were divided into 4 groups (i.e. Group-A for control, Group-B and Group-C for 300mg/kg and 500mg/kg oral doses of crude extract respectively and Group-D for standard). Each group comprised of 5 animals, weighing 25-30gm. Acetyl salicylic acid (Aspirin) as 300mg/kg orally was used as the reference compound. The crude drug and the acetyl salicylic acid were diluted in distilled water and administered orally. The control animals were treated orally with the same volume of saline as the crude extract.

Gross behavioural study

For monitoring the effects of crude extract of *Lipidium meyenii* and *Epimidium sagittatum* on central nervous system, the following procedure was adopted as described by Irwin *et al.,* 1968 and Debprasad *et al.,* 2003. Mice were divided in to seven groups each congaing five animals. The First three groups received vehicle, standard drugs diazepam and imipramine respectively and the remaining four groups received crude drugs at the dose of 300 and 500mg/kg. The animals were under observation visually by different responses immediately after the drug administration. The score of response were recoreded as no response (0), mild increase effects (+) moderate increase effects, strong increase effects (+++), very strong increase effects (++++). Mild decrease effects (-) moderate decrease effects (--),strong decrease effects (---), very strong decrease effects (-----).

Assessment of neuropharmacological activity

CNS activity was studied by open field test, cage crossing, head dip test, and swimming induced depression test. All the CNS related tests were performed in a calm and peaceful environment.

In each test, animals were divided into 4 groups (i.e. Group-A for control, Group-B and Group-C for 300mg/kg and 500mg/kg oral doses of crude extract respectively, and Group-D for standard). Each group comprised of 5 animals. Diazepam as 2mg/kg orally was used as standard. The crude drug and the diazepam were diluted in distilled water and administered orally. The control animals were treated orally with the same volume of saline as the crude extract. In all the tests observations were made after 30 to 40 minutes of oral dose of the test substance.

Open field activity

The open field apparatus designed in the laboratory consists of 76 X 76cm square area with opaque walls 42 cm high. The floor is divided by lines into 25 equal squares. Rats weighing 200 to 230gm were used as the test animals in this method. Testing was performed in a quite room under white light as described by Kennett *et*

al., 1985 and Turner 1965. Animals taken out from their home cages and were placed in the center square of the open field (one at a time). Number of Squares crossed with all four paws was counted for 30 minutes. Activities of control rats and drug treated rats were monitored in a balanced design to avoid order effect.

Head dip test

It is an exploratory test. A specially designed square shaped Head dip box having three holes in each side was used in this study. The observation was to count the number of head dips by the animal through these holes in specified time (Sanchez-Mateo *et al.,* 2002; Kasture, V.S., *et al.,* 2002 and Debprasad *et al.,* 2003). The head dip box in our laboratory is designed for mice. Mice weighing 25 to 30 gm were used in this test. The control and drug treated animals were placed individually in the head dip box and the observations were made for 30 minutes.

Cage crossing movement

The test performed on mice in a specifically designed having rectangular shape. Both control and treated mice were placed in to the cage and their cage crossing movements were noted in 30 minutes. The test is important for the motor activity of animal. This test was performed according to the method described by Florence *et al.,* 2000.

Forced induced swimming test

Forced induced swimming test was performed according to Sanchez Mateo *et al.,* 2002 and Turner 1965. This test determines the muscle and CNS activity of the crude extract. Mice weighing 25 to 30gm were placed individually for six minutes in the glass tub filled with water at room temperature up to the marked level. Mouse when placed in water suddenly starts to move its front and hind paws. The activity time of animal is determined with the help of stopwatch out of total observation time of six minutes.

Assessment of diuretic activity

Diuretic test

The modified method of Armando *et al.,* 1992 was used for the assessment of diuretic activity. Each mice was placed in an individual metabolic cage after the oral administration of test drug (Nalgene 170015, Techniplast, Italy) with the provision of water *ad libitum*. The cumulative urine output was measured (in ml) at 2, 4 and 6 hours. Furosimide 50mg/kg orally was taken as reference drug.

Social interaction

In this test mices were housed singly for five days prior to testing and social interaction was carried out in the suitable box. Control and experimental mice were intermixed and then observations were made (File, 1980).

Effect on body weight, reproduction and chronic toxicity studies

Modified methods were used for the assessment of body weight, reproduction and chronic toxicity studies as described by Adeneye *et al*., 2006 and Mukinda and Syce 2007. Mice of both sexes (25-30gm) were divided in to five groups each group consists of six animals. Three pairs of mice/cage were housed in well-ventilated room at 25°C. The animals had free access to water and same food. The crude extracts of both plants were administered orally (100, 200, 300 and 500 mg/kg body weight) for a period of 40 days. Control group received normal saline at the same time. The animals were observed for any change during the experiment. The signs of toxicity or death were also recorded.

Table 1: Chemical constituents identified by colour reactions with various chemical reagents

Types of chemical	*Lipidium meyenii*	*Epimidium sagittatum*
Triterpenes	-	-
Tannin	+	+
Saponin	-	-
Alkaloids	+	+
Carbohydrates	+	+
Proteins	++++	++
Sterols	-	+

Table 2: Assessment of analgesic activity by writhing test

Treatment	Dose mg/kg orally	Mean No. of writhes ±S.E.M	Inhibition (%)
Control	0.5 ml Saline	132.6±5.12	00
Crude extract of *maca*	300mg/kg	60.6±0.96	54.2*
	500mg/kg	44.6±1.08	66**
Crude extract of *Epimidium sagittatum*	300mg/kg	68.8±4.12	48.11
	500mg/kg	52.2±1.59	60.6*
Aspirin	300mg/kg	52.2±1.59	60.6**

STATISTICAL ANALYSIS

The significance of difference between means with ± SEM was determine by Dunnett's t-test at $P<0.05$ and $P<0.01$. All statistical procedure was performed according to the method of Alcaraz and Jimenez, 1989.

RESULTS

Chemical test

The presence of different chemical constituents in of *Lipidium meyenii* and *Epimidium sagitatum* were, identified by reactions with various chemical reagents mentioned in the experimental part. The reactions showed positive results for the presence of tannin, alkaloids, carbohydrate and sterols and protein while the triterepene

Table 3: Results of Gross behavioural activity

Type of response	Control	*Lipidium meyenii*		*Epimidium sagittatum*		Diazepam	Imipramine
		300mg/kg	500mg/kg	300mg/kg	500mg/kg	2mg/kg	10mg/kg
Nystagmus	0	0	0	0	0	++	0
Micturation	0	-,+	-,+	-,++	++	0	+
Irritability	0	--	--	-	--	--	0
Disorientation	0	0	0	0	+	+	0
Passivity	0	--	---	-	+	+++	--
Spontaneous activity	0	+++	++++	+	--	---	++
Pain response	0	-,+	--,+	+, -	-	--	+
Respiration	0	-,+	-,+	+, -	-	+	+
Limb tone	0	++	++	+	-	-	+
Enophthalmoses	0	+	++	0	-	+	0
Touch response	0	+	++	+	+	--	+
Righting reflex	0	+	++	+	+	-	+
Tail erection	0	++	+++	0	0	0	+

0: no effect or Normal, -, +: initially decrease than increase, +,-: initially increase than decrease

test is negative indicated the absence of these components (table 1).

Analgesic activity

The analgesic activity of *Lipidium meyenii* is given in table 2. The antinociceptive effect was evaluated in mice by the writhing test induced by acetic acid 0.6% (0.2 ml/20 g, i.p.). The extract at 300 and 500mg/kg orally caused an inhibition on the writhing response. Such effect were observed in mice pretreated with aspirin (*60.6%, $p<0.05$). The maximum inhibition of the nociceptive response (66%, $p<0.05$) was achieved at a dose of 500mg/kg.

Table 4: Assessment of Open field activity

Treatment	Dose mg/kg orally	Mean No. of Observations+ ±S.E.M
Control	0.5 ml Saline	58.6±1.61
Crude extract of *Lipidium meyenii*	300 mg/kg	66.2±1.86*
	500 mg/kg	81.6±2.55**
Crude extract of *epimedium sagittatum*	300 mg/kg	64.4±1.21*
	500 mg/kg	58.8±1.59
Diazepam	2 mg/kg	39±1.12
Imipramine	15 mg/kg	65.8±1.04

As shown in the table 3 and graph 2, the crude extract of *Epimidium sagittatum* shows 48.1% and 60.6% ($p<0.05$) inhibition of pain response at the dose of 300 and 500mg/kg respectively as compare to standard aspirin who's inhibitory response is 59.1%, $p<0.05$.

Gross behavioural activity

The results obtained from different experiments were presented in table 3. *Lipidium meyenii* produced spontaneous activity after 5 to 10 minutes of drug administration at 300mg/kg and at 500mg/kg dose produces more active response and alertness. However, the standard drug diazepam shows significant decrease in the motor activity and imipramine improve the motor activity (table 3). All these response of *Lipidium meyenii* when compared with standard drug imipramine a significant difference were observed.

The results of *Epimidium sagitattum* have interesting findings at 300 and 500mg/kg dose. At low dose the drug shows alertness and increase motor activity where as at high dose it has slight depressive response (table 3) but not as significant as diazepam.

Table 5: Assessment of head dip test

Treatment	Dose mg/kg orally	Mean No. of Observations ±S.E.M
Control	0.5ml Saline	25±4.75
Crude extract of *maca*	300mg/kg	38.6±2.16*
	500mg/kg	44.8±1.14**
Crude extract of *Epimidium*	300mg/kg	38±2.16*
	500mg/kg	30.2±1.14
Diazepam	2mg/kg	16.6±2.17**
Imipramine	15mg/kg	30.8±2.03

Neuropharmacological assessment

Open field, cage cross, head dip activity

In this test Diazepam significantly reduces the no. of square covered (table 4), cage cross (table 6) and head dip (table 5) ($p<0.05$). On the other hand Imipramine induced a slight increase in these parameters ($p<0.05$). Mice received 300 and 500mg/kg.

Administration of crude extract of *Lipidium meyenii* at 300 and 500mg/kg showed significant increment of number of square traveled ($p<0.05$), cage cross ($p<0.05$) and head dip ($p<0.05$). However the crude extract of *Epimidium sagittatum* showed interesting results. At 300

mg/kg there is stimulating response and at 500mg/kg slight depressive response was observed.

Forced induce swimming test and social interaction

All animals were treated with the crude extract of *Lipidium meyenii* and *Epimidium sagittatum* at the dose of 300 and 500mg/kg respectively. The results showed significant increase in mobility time with *Lipidium meyenii* at p<0.05 thus it possess dose dependant highly potent antidepressant effect (table 7) in comparison with imipramine standard drug.

Table 6: Assessment of Cage crossing activity

Treatment	Dose mg/kg orally	Mean No. of Observations ±S.E.M
Control	0.5ml Saline	25.67±1.604
Crude extract of *Lipidium meyenii*	300mg/kg	30±0.71*
	500mg/kg	45.2±0.86**
Crude extract of *Epimidium sagittatum*	300mg/kg	38±2.35?**
	500mg/kg	29.6±1.76
Diazepam	2mg/kg	09±0.317
Imipramine	15mg/kg	28±0.18

In case of *Epimidim sagitattum* (table 7) results are good in term of anxiolytic effect but not significant as standard drugs Diazepam and Imipramine at p<0.05. However its dual response of increase in mobility time at low dose and decrease in mobility time at high dose made useful for the management of complicated psychiatric disorders.

There were positive attitude in between mice when inte mix with each other upon administration of both crud extract but the intensity was varied (table 12).

Diuretics test

In this assay the crude extract of *Lipidium meyenii* did no show any significant diuretic activity (p<0.05) as compare to control and standard drug Furosemide, at 300 and 500mg/kg dose (table 8). Whereas *Epimidium sagtitatum* showed little diuretic effect at 300mg/kg and 500mg/kg respectively but also non significant at p<0.05 in comparison with standard drug (table 8).

Effect on body weight, reproduction and chronic toxicity studies

The crude extract of *Lipidium meyenii* and *Epimidium sagittatum* were found to be non toxic at the dose up to 500 (therapeutic doses) and did not cause any death in the treated animals. The Chronic oral administration o *Lipidium meyenii* caused no aggressive behaviour with al dosese, it greatly improves the fertility profile witl increased number of pups (table 9). No significant change in body weight was observed (table 11).

The crude extract of *Epimidium sagittatum* was also found to be non toxic at all doses and also shows positive sign for fertilization (table 10) and did not cause any death and change in body weight (table 11).

DISCUSSION

The crude extract of *Lipidium meyenii* (maca) at the dose of 300 and 500mg/kg showed 54.2 and 66% inhibition o

Table 7: Assessment of force induced swimming test

Treatment	Dose mg/kg orally	Mobility time Mean No. of Observations ± S.E.M	Immobility time Mean No. of Observations ± S.E.M
Control	0.5ml Saline	3.55±0.01	2.45±0.01
Crude extract of *Lipidium meyenii*	300mg/kg	4.30±0.07	1.7±0.07
	500mg/kg	5.22±0.07**	0.78±0.07
Crude extract of *epimidium*	300mg/kg	3.98±0.06	2.02±0.06
	500mg/kg	3.74±0.07*	2.26±0.07
Diazepam	2mg/kg	2.82 ±0.13	3.18 ± 0.074
Imipramine	1mg/kg	4.20 ± 0.23	1.40 ± 0.23

Table 8: Cumulative Urine out put in ml (Diuretic effect)

Treatment	Dose mg/kg orally	0.5 hr	2 hrs	4 hrs	6 hrs
Control	0.5 ml Saline	0.32±0.04	0.8±0.03	1ml±0.05	1.9±0.07
Crude extract of *Lipidium meyenii*	300 mg/kg	0.2±0.01	0.5±0.01	1.1 ±0.04	2.17±1.33
	500 mg/kg	0.25±0.004	0.45±0.01	1.24±0.05	2.53±1.36
Crude extract of *Epimidium* sagittatum	300 mg/kg	0.38 ±0.04	0.92±0.04	1.92±0.12	2.37±1.33
	500 mg/kg	0.46±0.024	0.98±0.074	1.22±0.16	2.63±0.36
Furosemide	10 mg/kg	1.02 ±0.06	3.04±0.093	4.98±0.07	5.27±1.86

Mean ±S.E.M, N = 5, Significance with respect to control (* = Significant results, ** = Highly significant results) p<0.05.

Table 9: Effects of oral administration of crude extracts *Lipidium meyenii* (therapeutic dose) for 40 days

Dose mg/kg	Mice Sex Male (3) /Female (3)	Total no. of dead	Survival < 2 month	Reproduction Symptom within 21 days	No. of pups
Control	0/6	2/6	"	---	----
100	0/6	0	"	+ 1/3	(4)
200	0/6	0	"	+ (1/3	(7)
300	0/6	0	"	++ (2/3)	7+9
500	0/6	0	"	++(2/3)	9+9

Table 10: Effects of oral administration of crude extracts *Epimidium sagittatum* (therapeutic dose) for 40 days

Dose mg/kg	Mice Sex Male (3)/Female (3)	Total no. of dead	Survival < 2 month	Reproduction Symptom Within 21 days	No. of pups
Control	0/6	1/6	"	---	----
100	0/6	0	"	+(1/3)	(4)
200	0/6	0	"	+ (1/3	(7)
300	0/6	0	"	+ (1/3)	(7)
500	0/6	0	"	+ (1/3)	(6)

Table 11: Effect on body weight after 21 days. (Average weight 25-30gm)

Dose	*Lipidium meyenii*		*Epimidium sagittatum*	
	Weight before drug	Weight After drug	Weight before drug	Weight After dry
Control	27.9	28.4	25	24
100 mg	25.4	26	28.4	27.9
300mg	29.3	29.90	26.3	27.4
500 mg	27.8	28	25.9	31

pain response induced by acetic acid in comparison, - standard drug aspirin produces 60 percent inhibition.

Whereas the crude extract of *Epimidium sagittatum* (horny goat weed) showed 48.1 and 60.6% response at the dose of 300 and 500mg/kg respectively.

Evaluation of abdominal constriction induced by acetic acid releases some endogenous mediators (Collier *et al.,* 1968) it is also believed that some proistanoids are also involved (Hunskaar and Hole, 1987). This drug reduces the nociceptive response at peripheral level and prominent effect is seen in late phase (Rosland *et al.,* 1990). Beside this there is increase in the sperm count and it improve fertility, smooth muscle relaxant prostaglandin such as PGE_1 enhance penile errection by relaxing the smooth muscle of Corpora Cavernosa. PGE_1 has been important for the treatment of impotency (Katzung Bertram G 1998). Presence of different amino acid protein and fats (table A), would plays an important role for the synthesis of catecholamines. Epinephrine and nor epinephrine have been involve in errection and ejaculation as well as inhibit diuresis due to its sympathomimetic action (Katzung Bertram G 1998). The possibility of mechanism is more through catecholamines but one cannot ignore the influence of prostaglandins. The effect of the crude extract of *Lipidium meyenii* at CNS is not excitatory but it improves the muscle activity (table 7) as well as enhances exploratory behaviour in the mice (open field, head dip and cage crossing). The diuresis is inhibited by the administration of crude extract of *L. meyenii*.

Mice were forced to swim; this test evaluates the depressive or antidepressant activity of drugs by mobility and immobility time. This drug (maca) significantly reduces the immobility time thus suggested that maca induces anti depressive activity which is more at 500 mg/kg dose. Significant differences were appeared by open field test among all test groups.

L. meyeni contains the high concentration of proteins and important nutrients, which provides the improved sexual function. It has arginine and histidine amino acid, which increases the sperm production, motility and improves ejaculation and orgasm therefore, enhances male fertility. *L. meyeni* also contain histidine amino acid (Valerio 2005). This histidine plays an important role in sexual function and helps for ejaculation and orgasm (Nemetallah, 1985).

In case of *Epimidium sagitattum* the crude extract also shows some analgesic effect which is less than *Lipidium meyenii*, it showed little stimulating effect at low dose (300mg/kg) but at increased dose (500mg/kg) it has little

depressive effect. The crude extract of Epimidium also promotes diuresis at 500mg/kg but not potent action was observed.

Social interaction shows positive behaviour with both extract, rather *Lipidium meyenii* increase the sniffing and following, it also increase sexual desires with out any aggressive behaviour in term of fighting and boxing. *Epimidium sagitattum* act as an anxiolytic and produces relaxation especially in female mice.

Reproduction cycle shows very interesting results in *Lipidium Meyenii* (table 9) with healthy pups who survive very well and more active as compare to control pups. These findings help the safety use for fertility and to improve body functions. Body weight neither increase nor decrease with *Lipidium meyenii* but there is slight increase in the weight at 500 mg/kg of crude extract of *Epimidium sagitattum* that may be because of its depression action on the CNS.

Epimidium sagitattum traditionally used in sexual disorders such as pre-menopausal problems, erectile dysfunctioning. The exact way that *E. sagitattum* works remain unknown. However, it may has adaptogenic effect which promote energy and decreases cortisol levels. In stress situation, increase cortisol levels causing fatigue and depressing sex drive. This drug helps to restore the levels of testosterone and thyroid hormone and improve sex drive. Some other studies showed that the horny goat weed also helps in reduction in bone loss, increased immune system function and muscle mass, and reduction in fat (Kuang *et al*., 1989). *E. sagitattum* stimulates sensory nerves especially in the genital region and also increases sperm production. Because of this effect the drug showed positive androgen effect on the genital organs (testes, prostate gland and muscles) in men and promotes sexual activity (Kuang *et al*., 1989, Liao *et al*., 1995).

CONCLUSION

In conclusion the results of *Lipidium meyenii* and *Epimidium sagittatum* are very good medicine for the treatment of reproductive disorders, *Lipidium meyenii* posses little central action and more peripheral effect in antinociceptive activity. It improve sexual activity possibly through sympathomimetic action and partly through prostaglandin, where as *Epimidium sagittatum* posses dose dependant central and peripheral effect which may be through other transmitter such as serotonin. These finding support the use of these potent medicines in reproductive disorders with out disturbing the behavioural profile (depressive or aggressive) as well as have good analgesic property. *Lipidium meyenii* has more advantage over alprostadil (because it causes pain: Katzung Bertram G. 1998). These results help for other investigations and for more precise mechanism.

Table 12: Assessment of Social interaction

Type of Social interactions	Control	*Lipidium meyenii*	*Epimidium sagittatum*
Sniffing	-	+++	+
Kicking	+	-	-
Following	-	+++	+
Bitting	-	_	-
Grooming	+	++	+

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Clinical Study

An evidence-based guide to epimedium extract , First Edition.Sarah E. Edwards, Inês da Costa Rocha, Elizabeth M. Williamson and Michael Heinrich.© 2015 John Wiley & Sons, Ltd. Published 2015 by John Wiley & Sons, Ltd.

Horny Goat Weed ***Epimedium spp.***

Mainly: *E. brevicornu* Maxim.; *E. koreanum* Nakai; *E. pubescens* Maxim.; *E. sagittatum* (Siebold & Zucc.) Maxim. Other species of *Epimedium* are used medicinally, including *E. acunatum* Franch and *E. wushanense* T.S.Ying (as unofficial substitutes of Epimedii herba)

Synonyms: *Aceranthus macrophyllus* Blume ex. K.Koch; *A. sagittatus* Siebold & Zucc. (=*E. sagittatum*)

Family: Berberidaceae

Other common names: Barrenwort; bishop's hat; epimedium; yin yang huo

Drug name: Epimedii herba

Botanical drug used: Aerial parts

Note: Based on the large number of species accepted in the Pharmacopoeia of China, in combination with the poor information that is generally available about the quality of products sold as horny goat weed, there can be no evidence-based use of a product with an acceptable quality. Therefore, it clearly cannot be recommended by a health care professional.

Indications/uses: To treat sexual dysfunction, particularly impotence in men and lack of libido in women. In traditional Chinese medicine, it is also used widely for osteoporosis. *Epimedium* species are used to treat a number of other conditions including rheumatic arthritis, menopausal symptoms and memory loss.

Evidence: There is limited evidence to support the use of epimedium to treat sexual dysfunction and osteoporosis, although it is known to contain potent phytoestrogenic compounds.

Safety: Tests in animal models have shown no serious toxicity issues, but human clinical safety has not been established. Epimedium should not be used concurrently with other phosphodiesterase-5 (PDE-5) inhibitors, or when PDE-5 inhibitors are contraindicated (e.g. cardiac arrhythmias), or during pregnancy and lactation.

Main chemical compounds: The main active constituents are the prenylated flavonoids, icariin and its metabolites, epimedins A, B, C, and the sagittatosides.

Other active compounds present include flavonol glycosides (of kaempferol, quercetin, myricetin); flavones (tricin, luteolin); biflavones (gingketin, isogingketin, bilobetin); lignans such as syringaresinol; alkaloids (e.g. epimediphine from *E. koreanum*); β-sitosterol (*E. sagittatum*, *E. brevicornu*); and a chalcone, isoliquiritigenin (from *E. koreanum*) (Ma et al. 2011; Pharmaceutical Press Editorial Team 2013; Zhang et al. 2013c).

Clinical evidence:

Sexual dysfunction: Limited clinical data are available on the effects of epimedium on erectile dysfunction. A small double-blind clinical trial was reported assessing an epimedium herbal complex supplement in 25 healthy men and 13 men who had used sildenafil (Viagra). The men were administered with the herbal complex for a minimum of 45 days. Daily use of the epimedium preparation was found to enhance sexual satisfaction to a greater extent than sildenafil (Ma et al. 2011).

Clinical Study

Bone health and osteoporosis in menopause: A five-year follow-up study of a herbal preparation of epimedium for prevention of postmenopausal osteoporosis and fragility fractures found that it was able to reduce postmenopausal bone loss, and also showed some potential for reduction in fragility fracture incidence (Deng et al. 2012). A randomised, double-blind placebo-controlled clinical study in 85 postmenopausal women with osteopenia (lower than normal mineral bone density, considered a precursor to osteoporosis), were treated with icariin 60 mg, combined with the isoflavonoids daidzein 15 mg, and genistein 3 mg, daily for 24 months. All patients were also given calcium 300 mg daily. A statistically significant, though small, increase in bone density was found in the test group and bone resorption markers were significantly decreased, compared to the control group (Zhang et al. 2007). Isoflavones are oestrogenic and so also have osteogenic activities.

Other oestrogenic effects: A study evaluating the effects of Epimedii herba water extract on blood lipid and sex hormone levels in 90 postmenopausal women found that after 6 months of medication, the extract decreased total cholesterol and triglyceride levels ($p < 0.01$) and significantly increased serum levels of oestradiol, compared with the pre-treatment level (Yan et al. 2008).

Pre-clinical evidence and mechanisms of action:

Sexual dysfunction: Icariin has erectogenic properties in animals, via phosphodiesterase type 5 (PDE-5) inhibition, and also neurotrophic effects *in vitro* and *in vivo* (Shindel et al. 2010). A study in male rats found increased sexual behaviour after treatment with epimedium in combination with four other medicinal plants. However, individual assessment of the herbs showed no improvement, indicating a possible synergistic action between them (Zanoli et al. 2008). A study in isolated rabbit corpus cavernosum (CC) smooth muscle showed that epimedium extracts could elicit a relaxation effect through activation of multiple targets on NO/cGMP signalling pathways. The study also found that they potentiated the effects of PDE-5 inhibitors (commonly used for erectile dysfunction), such as sildenafil and vardenafil. The crude extracts were found to have a greater potency than the purified compounds (Chiu et al. 2006).

Bone health and osteoporosis: Icariin is involved in the regulation of multiple signalling pathways in osteogenesis, anti-osteoclastogenesis, chondrogenesis, angiogenesis and inflammation. It has been reported to have the potential to be used as a substitute for osteoinductive protein-bone morphogenetic proteins, or to enhance their therapeutic effects, for bone tissue engineering as well as treatment of osteoporosis (Zhang et al. 2013b).

Other relevant effects: Icariin has phytoestrogenic properties and has been shown to promote the biosynthesis of oestrogen by aromatase (Yang et al. 2013). It reduced the levels of serum total cholesterol and low-density lipoprotein cholesterol, and reduced platelet adhesiveness and aggregation in atherosclerotic rabbits, demonstrating lipid-lowering effects (Zhang et al. 2013a). The alkaloid epimediphine has anticholinesterase activity (Zhang et al. 2013c), which together with the oestrogenic effects of other constituents, may support the use for memory enhancement.

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Interactions: There is conflicting evidence about a possible interaction with other PDE-5 inhibitors such as sildenafil (Viagra). *In vitro* evidence has suggested that epimedium potentiates PDE-5 inhibitors (Chiu et al. 2006), but a study of the effects of *E. sagittatum* extract on the pharmacokinetics of sildenafil demonstrated that the area under the concentration–time curve of sildenafil was significantly decreased in groups that received a high dose of epimedium extract, suggesting antagonistic effects (Hsueh et al. 2013). Co-administration with PDE-5 inhibitors should, therefore, be avoided until further information is available.

Another *in vitro* study found that epimedium is a potent inhibitor of cytochrome P450 isoforms (including CYP1A2, CYP2C19, CYP2E1, CYP2C9, CYP3A4, CYP2D6) and NADPH-CYP reductase, indicating a possible potential for interaction with other drugs, although the clinical significance is not known (Liu et al. 2006).

Contraindications: Epimedium should not be used during pregnancy and lactation as it has oestrogenic activity. Paediatric use is not appropriate. People with heart conditions should avoid using epimedium and long-term use is not recommended (Pharmaceutical Press Editorial Team 2013).

Adverse effects: In high doses (not specified), epimedium may have a stimulatory effect and cause sweating or a feeling of heat. Prolonged use of excessive amounts in animal studies was associated with decreased thyroid activity (Ma et al. 2011).

A case was reported of a 66-year-old man who developed heart arrhythmia and hypomania after taking a herbal sexual enhancement product containing epimedium. As it was a multi-ingredient preparation, and the man was predisposed to heart disease and possible mood disorder, it is unclear if this was caused by epimedium or another ingredient (Partin and Pushkin 2004).

Dosage: For products, see manufacturers' instructions. For the herb, the adult dose is 3–9 g dried aerial parts daily (Pharmaceutical Press Editorial Team 2013).

General plant information: According to a Chinese legend, a goat herder first noticed the qualities of the plant after he observed far more sexual activity in his goats after they ate it; hence the common name (Ma et al. 2011).

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Lepidium meyenii (Maca) – multidirectional health effects – review

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ABSTRACT

Lepidium meyenii, commonly known as Maca, is a Peruvian plant that grows high in the Andes, in areas over 4,000 meters above sea level. Its composition contains almost all of the essential amino acids and twenty of the essential fatty acids needed by man, as well as many vitamins, minerals and several sterols and glucosinolates. The specific and unique unsaturated acids and amides found only in this plant are the macaenes and macamides. Most valuable ingredients are contained within the hypocotyls. Maca comes in three forms, based on its root colour, yellow, red and black. Although used individually, consumption recommendations are usually for a mix of all three. Since Inca times, it has been considered as super food.

Although now mostly used in the form of a supplement, ongoing research does not exclude future applications of Maca as medicine. It is attributed to have an effect on male fertility (adding energy and vitality), and in regulating hormone secretion. In animal studies, Maca has been shown to have antioxidant, neuroprotective effects and antiviral activity. Moreover, it has been demonstrated to alleviate the effects of depression. In addition, there are reports that Maca reduces the development of cancer and osteoporosis, improves memory, facilitates concentration and alleviates the symptoms of menopause. The obtained results, however, require further analysis to confirm its effect. Currently, there is little information on toxicity, so there is a need for specialized research in this area, and on-going research concerns the most effective variety and form of preparation of Maca for administration to achieve best effects. The potential of Maca as medicine exists. The increasing pan-continental popularity of Maca has created the need for a better understanding of its action mechanisms.

INTRODUCTION

Maca, known in science as *Lepidium meyenii* Walpers, is a Peruvian plant growing naturally in areas above 4,000 meters in the Peruvian Central Andes. It belongs to the Brassicaceae family. The name *Lepidium meyenii* Walpers has been used since 1843, when German botanist Gerhard Walpers deposited the first holotype of this plant [1].

Maca contains many proteins, amino acids, fats and vitamins [2], as well as a variety of secondary metabolites such as maca ene, alkaloids (including maca amide), glucosinolates, and other components [3-5]. It is also a rich source of micro- and macroelements, including iron, calcium, copper, zinc and potassium. Maca has been used by local people as a food ingredient and in traditional folk medicine to enhance sexual function, fertility, energy, alertness, mental concentration, mood and physical immunity [6,7]. Maca is now marketed in Asia, Europe and North America.

Maca studies have been mostly conducted on animal models, although a few human trials exist in the literature. Due to its multifaceted effect as a natural remedy, it is receiving more attention and thus has become the subject of much research. Some review was carried out by GF Gonzales *et al.* [7], however, we have consolidated the latest reports in the context of the growing demand for Maca. This article, therefore, discusses the impact of Maca on humans, animals and selected cell lines. Our research has been carried

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out since 2007, and our listing includes the type of Maca, the particular plant part source and the type of extract. In our work, we list the studies in which Maca has been tested for its specific use as a sunscreen, for fertility needs, for treatment of erectile dysfunction, for enhancement of memory and for anti-viral activity. In such works, its antioxidant properties were also evaluated. A comparison of selected studies is shown in Table 1.

ULTRAVIOLET RADIATION PROTECTION

The protective effect of yellow Maca to ultraviolet radiation (UVR) was tested on 3-month-old male Holtzman rats. Herein, a topical boiled water extract had the strongest effect. In control animals, exposure to UVR rays resulted in the thickening of the epidermis. In experimental animals, epithelial height after dermal application of aqueous extract, were significantly lower in comparison with the control group. There were no differences in skin thickness between that of animals treated with aqueous extract and non-irradiated control. The effect was independent of the type of radiation [8]. The dose response was observed in the case of UVA, UVB and UVC radiation, with a better effect than that observed with commercial sunscreen. As the authors of the experiment suggest, the protective substances for the types of radiation used are the polyphenols and glucosinolates present in the Maca's aqueous extract. The authors also suggest that Maca is an effective agent for ameliorating UVC-mediated damage. Further research is, however, needed about the UV protection mechanism, but enough information exists to suggest its commercial application in sunscreens.

EFFECT ON SPERMATOGENESIS

The effects of aqueous Maca extracts on spermatogenesis have been the subject of research. Three types of Maca were tested: black, yellow and red. The study was conducted on 4-month-old male Holtzman rats. In the work, administration of boiled water extracts of yellow and red Maca as a gavage did not produce any effect, while a black Maca gavage seemed to have a beneficial effect on sperm counts and their motility [9]. Experimental results showed that after 42 days, sperm production was significantly higher, and while sperm motility was unchanged after 7 days of treatment with either of the three types of Maca [10,11], after 42 days of treatment with black Maca extract, the sperm motility was higher than in that of other groups. Testosterone and estradiol hormonal levels remained unchanged during the study.

Research by Ohta *et al.* provides additional information. Herein, young male Wistar rats of the experimental group were given in diet, a powdered Maca water-alcohol extract (a combination of yellow, black and red Maca, with the commercial name, MACAXS™) for 6 weeks. This study demonstrated that administration of a water-alcohol extract of Maca for 42 days elevated serum testosterone levels, although reports from other have not always confirmed this. The weight of the seminal vesicle also increased, but this could be due to enhanced testosterone levels as the seminal vesicle is sensitive to testosterone. The prostate gland remained unchanged, but serum testosterone concentration were elevated, suggesting that Maca can stimulate Leydig cells especially in the metabolic process of cholesterol [12,13]. Moreover, the weight of the rats increased progressively regardless of the diet used, suggesting that Maca does not affect b.w., although animal observations have also shown that Maca can stimulate appetite on a continuous basis. More recent studies, however, suggest that long-term administration of MACAXS™ induces only a temporary increase in serum testosterone in adult male rats [14].

Gasco *et al.* conducted an animal study using yellow, red and black Maca to evaluate the effects of these substances on daily sperm production and total sperm DNA concentrations. In the study, 3-month-old male Holtzman rats were used, as were water extracts of Maca. The results indicate that after 84 days of treatment, Maca modulates the number of spermatozoids at the level of reproductive tract, while in the epididymis and deferent duct, the number of sperm cell increases. No changes were observed in daily sperm production. These studies suggest that Maca may prevent sperm reduction in the epididymis as observed in animals without copulatory activity. The weight of the genitals did not changed, and no apoptotic changes in cells of the spermatogenesis series or DNA modification at the nucleus level [10] was reported.

In another randomized double-blind placebo-controlled study of 12 weeks, men aged 21 to 56 were involved. They were given Maca for 2, 4, 8 and 12 weeks. The results indicate that Maca did not modify testosterone levels, luteinizing hormone, follicle stimulating hormone, prolactin, 17-alpha hydroxyprogesterone and 17 beta-estradiol. The results suggest that Maca did not affect serum sex hormone levels in men [11].

CLINICAL STUDY-MACA

ANTIOXIDANT EFFECT

In a study, petroleum ether extracts of Black, yellow and purple Maca were administered at 100 mg/kg for 90 days to diabetic Wistar rats. Herein, previously identified in the extract analogies were macamides, the highest content of which was in the extract of black Maca. After 60-days, TBARS (thiobarbituric acid reactive substances) and carbonylated (CP) proteins were reduced, hence, lipid oxidation was also diminished in the diabetic rats [23]. Maca extracts also increased the activity of SOD (superoxide dismutase) and CAT (catalase) antioxidants, and enhanced the number of erythrocytes in the tested animals. Of all the types studied, the extract of purple Maca showed the strongest antioxidant activity in this experimental model.

In another study, Wistar rats underwent oral administration with a 1% Maca solution along with a high-sugar diet. The authors used rats with plasma glucose levels above 14.82 mmol/L. During the supplementation, very low-density lipoprotein (LDL), total cholesterol, serum triacylglycerol (TAG) levels, as well as VLDL (Very Low Density Lipoprotein) levels in the liver were observed. In addition, supplementation with Maca resulted in a decrease in blood glucose levels. The authors suggest that Maca may be used in the treatment and prophylaxis of chronic conditions characterized by atherogenic lipoprotein profiles, hepatic steatosis, antioxidant disorders and conditions with impaired glucose [23,24].

In yet one more study, soluble yellow Maca lipid extract containing macamides was evaluated. Herein, the studies was performed in rats treated at 100 mg/kg b.w. and the influence of lipid extract on swimming and energy depletion in animals was assessed. As a result, reduced serum LDH (lactate dehydrogenase) levels, muscle damage index, and TBARS were observed in lipid-induced muscle tissue lipid oxidation. However, the level of catalase in the liver and (glutathione) GSH antioxidant in muscle and liver were higher than in the control group that was not treated with Maca [25]. The study conclusion was that feeding the Maca extract for a period of 3 weeks significantly improved swim strength and endurance in a dose-dependent manner. The authors suggest that this effect depends on the effect of Maca extracts on suppression of post-exercise oxidative stress [25].

Table 1. Comparison of selected studies

Type of Maca	Plant Part	Origin	Type of extract	Study subjects	Results	References
Yellow	Dried hypocotyls	Pasco, Peru	mixed in water	Rats	Dermal protection against UV radiation was shown; the most effective - boiled maca	[8]
			water boiled extract			
Yellow, Red	Dried hypocotyls	Carhuamayo, Junin, Peru	water boiled extract	Rats	No effect	[9]
Black					Increase in sperm mobility	
Black	Dried hypocotyls	Carhuamayo, Junin, Peru	hydro-alcoholic extract	Mice	Inhibition of memory disorder	[16]
No data	Powdered root	Pampas Valley (Tayacaja, Huancavelica)	methanol extract	Cell lines	Inhibition of influenza viruses a and b	[22]
Black	Dried hypocotyls	Carhuamayo, Junin, Peru	water boiled extract, frozen and lyophilized	Mice	Improved learning and memory in mice	[17]
Black, Yellow, Violet	Dried plant	Juhua Village market Kunming province, Yunnan	petroleum ether extract	Rats	Strong antioxidant effects (purple Maca) in rats	[23]
Red, Yellow, Black	Dried hypocotyls	Carhuamayo, Junin, Peru	water-boiled extract	Rats	Increases in sperm cell count, increases in body weight in animal models	[10]
No data	Dried root	Kunming, China	polysaccharide mp21	Cell lines	Immuno-stimulating effects, increased macrophage activity	[26]
No data	Dried hypocotyls	Arequipa, Peru	methanol extract	Cell lines	Neuroprotective effects	[18,20]
	Leaves	Ramancancha, province of Junin, in the Junin Department		Rats		
No data	No data	Peru	no data	Mice	Regulation of autophagy proteins, slow down of cognitive decline associated with age	[19]
Yellow	No data	Ecoandino SAC Co. Lima, Peru	lipid extract	Rats	Improvement of physical condition by suppression of oxidative stress	[25]
No data	No data	Quimica Suiza, Peru	powder	Rats	Reduction of plasma cholesterol, VLDL, LDL and TAG	[24]
No data	Root	Junin, Peru	powder	Womans	Suppression of menopausal symptoms	[15]
No data	Root	Lima, Peru	powder	Men	No effect on the level of sex hormones	[11]
No data	No data	Linzhi, Xizang, China	petroleum ether extract	Mice	Antioxidant effect in brain tissue	[29]
Black, Red, Yellow	Dried bulb	MACAXS™ (TOWA Corporation K.K., Tokyo, Japan)	hydro-alcoholic powder extract	Rats	Stimulation of male sex hormones	[12]

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Conclusion

Fertrogen Pro is a combination of two potent ingredients clinically proven to increase a mans's ability and sustain an erection. Horny goat weed extract 500mg and Maca root extract 75 mg plays an important role with to inhibit PDE5 and dilation of blood vesels. Healthy blood flow to the genital area is a key for sexual Satisfaction. This combination has a beautiful synergistic efect on blood flow into the vessels from the damage that can occur from aging and enhances responsiveness, sexual stamina and enjoyment. Fertrogen Pro™ Registered trademark of Fertillmed Pharma Private Limited

Prescribing Information

Indications

Mild to severe Erectile dysfunction, Premature ejaculation and infertility.

Contraindications

No major contraindications recorded for this supplement

Dosage

2 tablets twicw a day for 12 weeks one tablet a day thereafter to maintain and sustain enhanced pleasure and performance

SoS : 1 Hour before intercource

Contraindications:

Epimedium should not be used during pregnancy and lactation as it has oestrogenic activity. Paediatric use is not appropriate.

Storage

Each Strip Contains 10 Tablets

Protect from moisture

Keep out of reach of children

Notes

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NOTES

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