UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE FARMÁCIA
TRABALHO DE CONCLUSÃO DE CURSO DE FARMÁCIA

PLANT BASED NATURAL SUPPLEMENTS TO ENHANCE PHYSICAL PERFORMANCE AND ANDROGENIC EFFECTS

ALINE MARTINS FAUSTINO

PORTO ALEGRE, 2024

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE FARMÁCIA

TRABALHO DE CONCLUSÃO DE CURSO DE FARMÁCIA

Aline Martins Faustino

PLANT BASED NATURAL SUPPLEMENTS TO ENHANCE PHYSICAL PERFORMANCE AND ANDROGENIC EFFECTS

Trabalho de Conclusão de Curso apresentado ao Curso de Farmácia da Universidade Federal do Rio Grande do Sul como requisito para obtenção do título de grau de Farmacêutico.

Orientador: Prof. Dr. Walter Orlando Beys da Silva
Co-orientadora: Farmacêutica Camila Innocente Alves

Porto Alegre, 2024

AGRADECIMENTOS

Eu sou muito grata a todos que passaram pela minha vida e contribuíram de alguma forma para quem sou hoje, mas sou grata especialmente a quem esteve comigo nessa jornada nos últimos meses.

Primeiramente, agradeço ao meu orientador, Walter. Obrigada por confiar e me incentivar, com um conselho ou uma piadinha de alívio, sempre exercendo o seu papel nos orientando no trabalho e especialmente na vida. Também queria agradecer à professora Lucélia, por sempre ser tão receptiva e deixar o ambiente aconchegante e tranquilo, com cheiro de café quentinho. Muito obrigada ao meu laboratório, a todos que me ajudaram de alguma forma ou que ouviram meus desabafos. Sou muito grata pelo ambiente e pela troca que temos.Especialmente para minha co-orientadora, amiga e colega de estágio, Camila. Eu não tenho palavras para agradecer todo o apoio que tu me dá, seja no laboratório ou na vida, sempre está presente.

Aos meus amigos, dentro e fora da faculdade, que acompanharam meus últimos anos me dando apoio. Especialmente para minha amiga Bibiana, que está comigo desde a primeira semana da graduação, segurando minha mão e enfrentando esses anos comigo. Que bom que nossos caminhos se cruzaram, eu sou muito grata por ter a tua amizade e companheirismo em todos os momentos, minha dupla.

Por último, à minha família, que proporcionou que eu pudesse chegar até aqui. Ao meu padrasto (pai) Moisés, que nunca mediu esforços para fazer meus sonhos possíveis. À minha mãe, que sempre me deu asas para voar e impulsionou todos os meus voos desde então. Todos os agradecimentos do mundo pra ti.

Muito obrigada.

APRESENTAÇÃO

Esse Trabalho de Conclusão de Curso foi redigido sob a forma de artigo ao qual foi elaborado segundo as normas da revista Chemistry & Biodiversity, apresentadas em anexo.

Plant based natural supplements to enhance physical performance and androgenic effects

Aline Martins Faustino[1], Camila Innocente-Alves[1], Julia Sant'ana de Fraga[1], Yohana Porto Calegari-Alves[1], Walter Orlando Beys-da-Silva[1]
[1]Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul

Abstract:
The benefits of natural supplements, exercise and healthy diet for longevity have been demonstrated by several studies in recent years. Plants such as Tribulus (*Tribulus terrestris L*), Ashwagandha (*Withania somnifera L*), Long Jack (*Eurycoma longifolia Jack*) and Maca Peruana (*Lepidium meyenii*) are examples used in supplements aiming to increase testosterone levels, improve fertility and sexual function. These supplements promise benefits such as increased libido, energy for exercise and improved bone density. Although their effects are popularly known, especially their aphrodisiac effects, there are still assumptions and lack of experimental validation about their mechanism of action. In order to fill these gaps, this review aimed to gather information about Long Jack, Tribulus, Ashwagandha and Maca Peruana that can establish current scientific knowledge about their potential use linked to sexual function and exercise performance, included their potential mechanismo of action, phitocemistry and experimental and clinical evidences.

Keywords: natural products, biological activity, Eurycoma longifolia, Tribulus terrestris, Withania somnifera, Lipidium meyenii, sexual function, physical performance

Abbreviations: testosterone replacement therapy (TRT), hypothalamic-pituitary-gonadal (HPG)

1. Introduction

Currently, there has been a significant increase in the search for natural alternatives to improve health, physical performance and lifestyle. This trend has been growing in recent years, corroborated by new studies confirming the benefits of natural supplements, physical exercise and healthy eating for longevity [1]. At the same time, plants have always contributed extensively to the development of traditional and modern medicine, and for a long time natural products were the only medicines available, playing an important role to this day in the discovery of new drugs.

Medicinal plants have diverse therapeutic applications due to their bioactive molecules, resulting in activities such as cardiovascular agents [2], anti-inflammatory compounds [3], anticancer agents [4], antimicrobial activity [5] and aphrodisiac activities [6]. The use of herbal therapies can be safer in many ways, as they have fewer adverse effects and a potential lower risk of cytotoxicity [7]. One example is hormone regulation therapies, where supplements are gaining popularity as natural alternatives to increase hormonal levels, such as testosterone [8].

Looking at the composition of these supplements, many plant names are repeated, such as Tribulus (*Tribulus terrestris* L), Fenugreek (*Trigonella foenum-graecum*), Ashwagandha (*Withania somnifera* L), Long Jack (*Eurycoma*

longifolia Jack), Turkesterone (*Ajuga turkestanica*) and Peruvian Maca (*Lepidium meyenii*). These plants are often used in these products because of their associated ethnopharmacological knowledge that links those plants to aphrodisiac activities, which would enhance fertility, improve sexual performance, treat erectile dysfunction, promote vasodilation and increase testosterone levels [9].

Recent studies indicate that the market is popularizing “T boost” supplements based on one or more plants in the same formulation promising to increase testosterone production naturally [10]. In fact, the food and drug administration (FDA) classifies that “unlike drugs, supplements are not intended to treat, diagnose, prevent or cure disease” [11]. The supplements promise improved mood, more energy for physical exercise, increased libido and fertility, among other benefits. The main target audience is men, but the market is also expanding to women.

The expected “testosterone boost” mimics the effects of testosterone in human body, such as sexual actions, effects on protein synthesis, anabolic and anticatabolic effects, generating improved muscle hypertrophy and increased bone density, as well as improved sexual function [12]. On the other hand, low testosterone levels can lead to reduced libido, erectile dysfunction and male infertility. In addition, low testosterone levels can cause obesity, reduced lean mass, decreased bone density, fatigue and depression [13]. For individuals presenting low testosterone levels, testosterone replacement therapy (TRT) might be the first therapeutic option in many cases. However, TRT is contraindicated for many patients who suffer from prostatic hyperplasia, high hematocrit concentration, or who have sleep disorders such as apnea [13,14].

Due to the limitations of TRT and the need for fewer adverse effects in treating those outcomes linked to low levels of testosterone, medicinal plants have become even more popular as therapeutic alternatives worldwide. The effects of these plants are popularly known and proven mainly for their aphrodisiac effects, but there are still many assumptions about the mechanism of action of each of them. In order to fill these gaps, this review aims to gather scientific data on the medicinal plants Long Jack (*E. longifolia* Jack), Tribulus (*T. terrestris* L), Ashwagandha (*W. somnifera* L) and Peruvian Maca (*L. meyenii*) that could establish the current knowledge on the proven effects linked to sexual function and exercise performance. Information on their origins, doses, phytochemical characterization and potential mechanisms of action for androgenic effects, as well as the evidence supporting their effects will be addressed. Some of the main ones used in Brazil.

2. Medicinal plants

The use of plants for medicinal purposes predates recorded history. Traditional medicine, is defined as “skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness” (World Health Organization, 2023). It includes the indigenous practices and even popular Indian Ayurvedic medicine among the Asian countries, passed down through many centuries, spanning generations in the use of plants for healing purposes [15].

The application of herbal based medicine has long been approved worldwide, and their effectiveness is proven for various conditions. In 2011, WHO estimated that

80% of people worldwide rely on herbal medicines for some of their primary health care needs [16]. According to the WHO, in 2021 approximately 40% of pharmaceutical products have a basis in natural products, and landmark drugs are derived from herbal medicine or vegetable extracts. The plants described in Section 1 are sold mainly in the form of capsules and tablets as natural supplements, rather than the plant itself or its extract. Traditional medicine, as well as complementary and alternative medicine, make a well-established contribution to our health and are preliminary steps to the development of pharmaceuticals and nutraceuticals products.

2.1 Long Jack, *Eurycoma longifolia,* and its popular uses

E. longifolia Jack is a plant belonging to the Simaroubaceae family, of the *Eurycoma* genus. Popular in the Asian continent, Malaysia is described as the country of origin, but it is found throughout Southeast Asia such as Indonesia, Vietnam and the Philippines (Gimlette and Thomson, 1977, [17]. Its use dates back to the indigenous peoples of the region with use for various purposes, but it is currently gaining popularity in the West, proving effectiveness for various therapies that will be discussed below. This plant presents different popular names depending on the region and country, such as Tongkat ali, Malaysian Ginseng or Nature's Viagra. In different countries it has become popular under the name “Long Jack”, which was used in this work [17].

About its morphology, it is a tree with a height of between 10 and 18 meters. It has long leaves with axillary inflorescences, reddish in color with the presence of glandular trichomes, as is typical of this family. The part of pharmacological interest with the highest concentration of bioactive substances are the roots, characterized by their yellowish-white color and long, twisted appearance, similar to a "cane", with a characteristic smell and very bitter taste. In Asia, compounds based on *E. longifolia* roots are among the best known and most widely used medicinal herbs [18].

As previously mentioned, the use of *E. longifolia* has always been present in traditional indigenous medicine. Its roots are used to produce aqueous and alcoholic extracts for different purposes, such as digestive tract discomfort, fever, jaundice and its main and best-known effect, aphrodisiac [17]. Some studies have raised hypotheses about its possible antimalarial effects, after tests with *E. longifolia* extract showed favorable activity for inhibiting an isolate of *Plasmodium falciparum* in vitro tests, proving to be effective compared to chloroquine-resistant strains. [19]. It has also been found to have cytotoxic activity against cancer cell lines as observed by Zakaria et al. in liver carcinoma cells (HEPG2) where apoptosis was induced, showing promising results [20].

Regarding its aphrodisiac activity, the search for substances to increase virility and sexual prowess has always existed and in Asia *E. longifolia* is considered one of the best known natural aphrodisiacs, widely used for these purposes, specifically the extract made from the roots to potentially increase testosterone levels in men [17,21]. Consequently, the relationship between androgenic effects and physical performance has been extrapolated,, along with the interest in supplements to increase muscle mass, which has been growing in recent years [22]. Long Jack is currently used as dietary supplements to increase libido, lean mass growth and hormonal balance. Studies show that it is effective at regulating hormone levels such as cortisol and testosterone, which contributes to improving specific performance.

2.1.1 Chemical composition

In relation to the components that provide the pharmacological activities proposed by *E. longifolia*, especially with regard to androgenic effects, studies discussing the plant's chemical composition were analyzed. *E. longifolia* has a broad spectrum of bioactive compounds in all its parts, but the greatest focus is on its roots, which have the highest concentration. Kuo et al. (2004) analyzed all the active components present in the roots using mass spectrometry (LC-MS/MS). Sixty-five phenolic compounds were detected in the roots of the plant, these included quassinoids, alkaloids, cantin-6-one alkaloids, β-carboline, triterpene, truecaller, squalene derivatives, eurycolactone, eurycomalactone, leurycolactone, biphenyl and bioactive steroids [23,24]. Most abundant are the quassinoid compounds present in the plant, which are triterpene lactones characteristic of the Simaroubaceae family of plants (Curcino Vieira and Braz-Filho 2006). The most abundant quassinoid in Long Jack is eurycomanone (Figure 1).

Low et al (2013) discusses the presence of quassinoids present in the extract of *E. longifolia* and the relationship of eurycomanone with increased spermatogenesis, the study hypothesizes that the compound acts by inhibiting the conversion of testosterone aromatase to estrogen and in high doses is able to inhibit phosphodiesterase suggesting the relationship that eurycomanone is related to the aphrodisiac effects of the plant, and may be related to increased testosterone and improved sexual function. [25]. It is important to note that the compounds found in *E. longifolia* can vary according to the temperature and region where the plant was harvested, as detected by liquid chromatography of different extracts from plants grown at different temperatures [25,26].

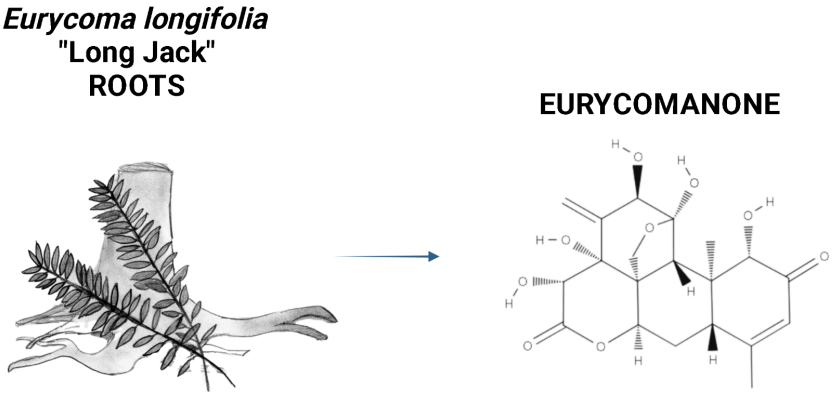


Figure 1. *E. longifolia* plant and chemical structure of Eurycomanone, the main compound described as responsible for its pharmacological action. Molecules were obtained using Molview (https://molview.org/)

2.1.2 Potential mechanism of action

The mechanism of action of *E. longifolia* has not yet been fully elucidated. Study in vivo (Low et al 2013) have speculated that a potential action on the hypothalamic-pituitary-gonadal (HPG) axis would be a relationship between the quassinoids mentioned in Section 2.1.2 with stimulation of sex gonadotropin

production, increasing secretion by Leydig cells, this hypothesis to light, as eurycomanone was seen in the leydig cells of treated male rats, highlighting the possible mechanism of action. [25]

2.1.3 *In vivo* and Clinical studies

The pharmacology of extracts based on *E. longifolia* has been the subject of numerous studies [21,27,28], especially regarding its aphrodisiac functions and androgenic effects that lead to increasing sexual potency and fertility. Studies such as Ang and Sim (1997) analyzed the action of *E. longifolia* in increasing libido and sexual function in rats of active sexual age. Different doses of extract at different concentrations prepared with different solvents were tested for ten consecutive days. To analyze libido *in vivo,* a protocol was used to observe the frequency of mouthing, the frequency of intromission and ejaculation frequency during the cupula of the animals after treatment. The results indicate that treatment with *E. longifolia* extract in male rats increased sexual function, with no difference between the doses and solvents used. [21]. Ang and Ngai (2001) evaluated the chronic use of *E. longifolia* in non-copulating male rats, considered old rats at doses of *E. longifolia* root extracts for twelve consecutive weeks. To analyze the increase in libido, the male rats were placed in an electric copulation cage during the dark phase of the light cycle, analyzing how much the aversive stimulus would prevent them from copulating with their family. Thus, they found that *E. longifolia* extract is a potent sexual stimulant, increasing sexual libido in aged rats, also showing an improvement in the animals sexual performance [27].

As already mentioned, there are still many gaps, especially in relation to muscle and supplements based on *E. longifolia.* To better understand this relationship, Ang and Cheang (2001) analyzed ani muscle in castrated and non-castrated male rats and testosterone stimulation in rats treated with different *E. longifolia* doses. This muscle is associated with the pelvic floor and may contribute to maintaining erection and controlling male ejaculation. Therefore, the improved muscle density may be related to improved sexual performance. After euthanasia, an increase in the levator ani muscle was observed; all doses showed positive effects on the animals' muscles. Therefore, this provides further support for the plant's aphrodisiac functions [28].

Another potential use of *E. longifolia* is the treatment of male infertility, knowing the relationship that the high concentration of estrogen, acting directly on the Leydig cells, suppresses testosterone levels, thus leading to a decrease in spermatogenesis which leads to infertility and infertility [29], Wahab et al (2010) carried out a study on male rats, determining the effects of *E. longifolia* in neutralizing estrogen with the aim of improving the animals fertility. Epididymal sperm counts and histological analysis were carried out. The animals treated with *E. longifolia* showed an increase in the percentage of epididymal sperm compared to the other group and inhibited the effects of excess estrogen, and can also be used in the treatment of infertility [30].

As described, the experimental evidence does not provide a potential and concrete therapeutic dose, possibly because the amount of components in the roots may vary. However, studies such as those show that the mechanism of action of *E. longifolia* appears to be through pro-androgenic effects, acting directly on the

hypothalamic-pituitary-gonadal axis. Even with gaps, the studies are in accordance with popular medicine, indicating an action that leads to improved sexual function.

2.2 *Tribulus terrestris* and its popular uses

Tribulus terrestris L. is a plant belonging to the family Zygophyllaceae, considered a weed, common in pastures and roads, typical of hot environments [31]. This plant is found in several countries and it is not possible to pinpoint its place of origin. It is found in the Mediterranean region of Europe, South Africa, Australia and India, and adapts easily to desert climates in general. With its wide distribution, it ends up being known by different names, such as puncture vine, Gokshur, Kokullak, Neringil, and Khare khasak [31].

In terms of its morphological characteristics, the *T. terrestris* plant can measure between 10 and 60 cm. It has simple or sparsely branched stems, opposite, irregular and paripinnate leaves with 5 to 8 pairs of leaflets and small flowers with bright yellow petals [31]. The main source of pharmacological interest lies in its fruits, which are hard, rough, star-shaped knots with thorns [32]. As mentioned above, in therapeutic use, the focus is on its dried fruits for preparations of aqueous and alcoholic extracts, which are rich in biological properties such as the presence of steroid saponins and flavonoids, components related to their activities [33].

Regarding the origin of its use, it is assumed that it began in traditional oriental medicine, being considered an ancient and valuable plant for health, described in the Shen-Nong Pharmacopoeia, one of the oldest pharmacological records in the world [34]. Initially, its main use was linked to a great aphrodisiac potential, but it is also widely used for edema, abdominal distension and cardiovascular diseases [35,36]. Having been used for centuries in oriental medicine, in the 1980s it began to attract attention in the West as a potential testosterone booster, promising increased libido for physically active men. With its widespread use, it is now considered one of the most widely marketed supplements of its kind, and is a major target for athletes and bodybuilders. It is often used as an alternative to therapies based on androgenic-anabolic steroids, such as TRT [37]. In addition to aphrodisiac effects, some studies report promising effects of *T. terrestris* on systemic cardiovascular problems, reduction of edema and ascites, analgesic effects, abdominal distension, diuretic, astringent, antibacterial effects. [35].

2.2.1 Chemical composition

The phytochemical composition of *T. terrestris* presents a broad spectrum of active compounds, being rich in steroidal secondary metabolites, such as flavonoids, tannins, alkaloids, and the main compound present in *T. terrestris,* steroidal saponins [38]. Saponins are mostly found in its dried fruit and are the main glycoside present in *T. terrestris*, divided into two main groups: furostanol and spirostanol. The saponins in the furostanol group are characterized by the presence of an additional spiral ring, such as protodioscin, which makes up 45% of the plant [31,35]. Spirostanol, on the other hand, has a spirostane nucleus without a spiral ring, and because of this chemical structure it serves as a raw material for the synthesis of steroid hormones (Figure 2), such as progesterone, cortisol and cortisone ([32,33]. This is one of the most studied components of *T. terrestris*, known for its aphrodisiac properties, acting to increase the conversion of testosterone into dihydrotestosterone, responsible for

stimulating sexual desire, the production of red blood cells by the bone marrow and muscle development, contributing to improved circulation and the oxygen transport system [32,33].

Studies show that the chemical content of *T. terrestris* is variable and can fluctuate due to pre-flowering and flowering periods, as well as differences in composition in different regions of the same country. [39] Considering these phytochemical variations, it is estimated that the minimum concentration of saponins present in supplements to obtain expected pharmacological effect is 40% [39]. The doses recommended by the Indian government are 3 g in capsule form or 20 to 30 g for decoction [33,40].

Regarding other compounds present in the plant, using high-performance liquid chromatography (HPLC), substances such as kaempferol, kaempferol-3-glucoside, kaempferol-3-rutinoside and tribuloside [kaempferol-3-O-β-D-(6-p-coumaroyl) glycosides] have been identified from the leaves and fruits of this plant. These compounds include caffeine derivatives, quercetin glycosides, including caffeoyl derivatives, quercetin glycosides and kaempferol glycosides in leaf extracts of four *Tribulus* species [34].

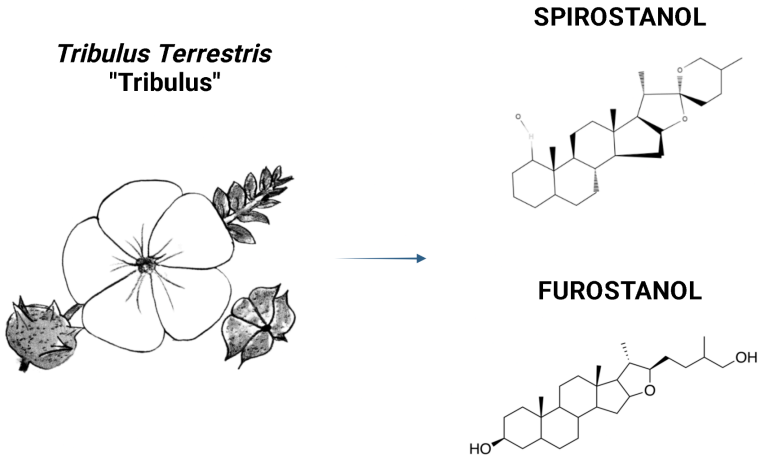


Figure 2. *Tribulus terrestris* plant and the structures of Spirostanol and furostanol saponins, the main chemical compounds responsible for its pharmacological action. Molecules were obtained using Molview (https://molview.org/)

2.2.2 Potential mechanism of action

There is no consensus on the specific processes involved in the possible mechanisms of action of *T. terrestris* extracts, but it seems that there is an increase in the release of important hormones, such as gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which are crucial for testosterone production [39]. In addition, studies such as. demonstrate that *T. terrestris* can raise intratesticular testosterone levels, resulting in the production of nitric oxide, a vasodilator that improves blood flow to the erectile tissue, facilitating erection. In this way, *T. terrestris* can provide significant benefits for sexual disorders, increasing libido and erectile function. [41]

However, there is still no clear agreement on the specific mechanisms by which *T. terrestris* influences sexual performance and spermatogenesis. The most

accepted theory is that the steroidal saponins present in *T. terrestris* extracts, especially protodioscin, increase androgen production by stimulating the release of LH by the pituitary gland. Another hypothesis suggests that the active components of *T. terrestris* may be enzymatically converted into weak androgens, such as dehydroepiandrosterone (DHEA), which would then be transformed into more potent androgens, such as testosterone, in the gonads and peripheral tissues [31]. However, the changes in endogenous hormone levels following *T. terrestris* administration are still the subject of debate [42].

2.2.3 *In vivo* and Clinical studies

Most studies involving *T. terrestris* focus on the plant's aphrodisiac-related effects. As mentioned above, its mechanism of action has not yet been fully elucidated. Studies such as Adaikan et al (2000) analyzed the effects of *T. terrestris* extract on rabbit muscle, due to its similarity to human muscle [35].. The results showed that there were effects on the pro-erectile smooth muscle after oral treatment. Also, it showed that there was a decrease in nitroglycerin in the tissue relaxation of acetylcholine, increased release of nitric oxide by the endothelium and nitrergic never ending. An increase in serum testosterone levels and erection time in male albino rats was also reported. [35,43].

As mentioned previously, one of the main saponins in *T. terrestris* is protodioscin. Gauthaman et al (2002) analyzed the effects of a saponin rich *T. terrestris* extract compared to testosterone administration in castrated male rats. After the treatment period, mount frequency, intromission frequency, mount latency, intromission latency, ejaculation latency, post- ejaculatory interval were analyzed through compilation with females. Accordingly their results the aphrodisiac effects of *T. terrestris* extract are significant even in castrated rats. [44]

Since studies [43,45] have obtained positive results in the improvment of the sexual function of rats treated with *T. terrestris,* Singh et al (2012) analyzed the sexual function of sexually sluggish rats treated with lyophilized extract of the fruits of *T. terrestris* (LAET) Mount latency, introduction latency, ejaculation latency, mount frequency, intromission frequency and penile erection index were assessed. Their results showed that *T. terrestris* seems to reverse the sexual dysfunction of rats caused by age and could be a possible alternative treatment for sexual dysfunction in men. [43]

T. terrestris extract was also tested clinically in humans in a randomized, double-blind placebo-controlled, phase IV clinical trial (Kamenov et al. 2017). The study included 180 men aged 18-65 years who reported mild to moderate erectile dysfunction, with or without hypoactive sexual desire disorder. The aim of the study was to analyze the plant's performance in treating these disorders, as well as to evaluate its safety profile. For this purpose, the commercial extract Tribestan 250 mg was used, with standardized furostanol saponins (≥ 112.5 mg). After 12 weeks of treatment, sexual desire and erectile dysfunction were assessed using the International Index of Erectile Function (IIEF) and there was found a change in the IIEF score, indicating an improvement in the patients' sexual function. Biochemical tests and blood pressure analysis were carried out on the patients every month of the intervention and all parameters remained stable and testosterone levels did not change. Accordingly, patients suffering from sexual dysfunction may benefit from treatment with *T. terrestris,* achieving a significant improvement in libido and sexual function [45].

The study by Singh (2012) found an increase in testosterone in the group that received *T. terrestris*, which may be related to the plant's phytochemical studies that link the increase in testosterone levels through compounds such as protodioscin and protogracilin, but further studies are still needed, leaving gaps. Although the studies by Adaikan, Gauthaman and Kamenov show that the administration of *T. terrestris* has significant benefits for sexual function in humans, we cannot say that there is a direct benefit for physical performance, but it may favor muscle development based on the physiological actions of testosterone that are already known.

2.3 *Withania somnifera L.* "Ashwagandha" and its popular uses

Withania somnifera L. is a plant belonging to the Solanaceae family. As for its geographical distribution, it prefers tropical and subtropical temperatures all over the world and can be found in several countries such as South Africa, the Middle East, Sri Lanka, India and China frequently, and less frequently in European countries [46]. Globally, it is known by various popular names, such as “Asgand”, Ashwagandha and Indian ginseng [47].

Morphologically, *W. somnifera* is a small evergreen shrub, no more than 2 meters high and 1 meter wide, with alternate, elliptical, green and glabrous leaves. Its spherical, orange-red, visually distinctive fruits contain numerous kidney-shaped seeds [47]. The roots are robust with secondary fibrous branches and have a characteristic smell and taste [48].

The plant has pharmacological properties due to its concentration of chemical components which will be discussed in section 2.3.1. Traditionally, extracts of the dried plant are produced to treat various diseases. The flowers have diuretic, astringent, purifying and aphrodisiac properties, while the leaves are used to treat fevers [49]. The seeds have medicinal properties, such as improving sperm count and testicular growth, being anthelmintic and helping to remove white spots from the cornea. However, the fruits are commonly used against various types of skin ulcers, skin diseases and carbuncles [49]. In addition, Ashwagandha has anti-inflammatory [50], antimicrobial [51], anti-arthritis [52] and anti-cancer [53] benefits.

In addition, the use of *W. somnifera* is well known for improving physical performance and treating anxiety, stress and sleep-inducing disorders [46,54,55]. Its name “somnifera” derives from the Latin word for “sleep inducer” and is one of its oldest popular uses due to its anti-stress properties [46]. As far as improving physical performance is concerned, it has yet to be elucidated. It may be related to a reduction in potentially stressful agents, or in anti-inflammatory and oxidative pathways, and may be an increment in improving physical performance [54].

2.3.1 Chemical composition

Regarding the phytochemistry of the plant *W. somnifera*, it is rich in bioactive compounds such as alkaloids, steroidal lactones, flavonoids, among others [48].The major pharmacologically active compounds are the steroidal lactones, known as withanolides. These are primarily divided into Withanolide D and Withaferin A [48]). Both compounds feature a lactone ring in their chemical structure, with Withaferin A distinguished by an epoxide termination on ring A, differentiating it from Withanolide D (Figure 3) [48]. Studies such as those by Paul et al (2021) which gather the chemical

information and their functions connect the compounds with their pharmacological activities associated with Ashwagandha, including its aphrodisiac, anti-inflammatory, anti-cancer, anti-stress and neuroprotective effects.

In addition, notable alkaloids include Somniferin, Somniferin and Somnin, which exert effects on the central nervous system, demonstrating cholinergic activity and promoting neurogenesis by inducing sleep and anti-stress action [56]. The phytochemical identification of *W. somnifera* also highlights the presence of fatty acids, fatty alcohols, volatile oils, palmitic acid and linoleic acid (Saleem et al. 2020). The roots of *W. somnifera* contain reducing sugars, starch, glycosides and withaniol acid [48]

The chemical composition of Ashwagandha can vary depending on factors such as the part of the plant used, the geographical location where it is grown and the extraction method used [57].

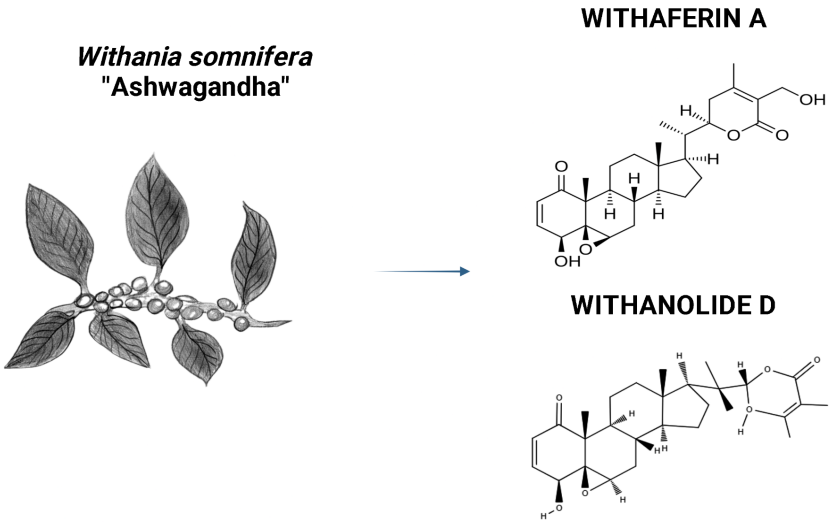


Figure 3. Representation of the plant *W. somnifera* and structures of Withaferin A and Withanolide D, the main chemical compounds responsible for its pharmacological action. Molecules were obtained using Molview (https://molview.org/)

2.3.2 Potential mechanism of action

Currently, there are no studies describing the mechanisms of action of *W. somnifera* for its uses, especially in association with physical performance in humans. However, as described in section 2.3.1, the effects on physical exercise may be related to the antioxidant properties of this plant [58]. By acting on reactive oxygen species (ROS) for the processes of physiological adaptation to physical exercise; however, excessive training, low energy availability or inadequate sleep hygiene can increase the production of ROS [54]) which can negatively affect muscle performance.

On the other hand, it has also been argued that the improvement in sexual and physical performance may be related to its anti-stress effects, leading the body to relax and providing better performance in both situations through endocrine pathways, regulating and stimulating the production of hormones such as androgens

[48] Looking at studies such as Sharpe, he analyzed the presence of active compounds from *W. somnifera* in leydig and sertoli cells, which may have some relationship with the hypothalamic-pituitary-adrenal axis, but there are still gaps that do not make its mechanism clear [48,59].

2.3.3 Clinical study

In relation to the effects on improving sexual performance, research indicates that active compounds in the plant, such as withanolides, can positively influence the endocrine system, helping to regulate sex hormones [48]. Studies such as Dongre et al 2015 and Chauhan et al. 2022 have shown that supplementation with Ashwagandha can increase testosterone levels, a hormone crucial for sexual desire in both men and women, making it safe for use by both sexes [60,61].

The study by Dongre (2015) investigated the effects of *W. somnifera* on sexual function disorders in women in a randomized pilot study with 50 women between the ages of 21 and 50 who were experiencing sexual difficulties. The participants' sexual function was analyzed using two psychometric scales, the Female Sexual Function Index (FSFI) and Female Sexual Distress Scale (FSDS) questionnaires. The results were promising, with significant improvements in the group treated with Ashwagandha. Compared to placebo, there was a 122.67% increase in sexual desire, there was an increase in levels of arousal, lubrication, orgasm, and sexual satisfaction with an overall improvement of 75.83% in sexual function as assessed by the FSFI. These results are in line with the hypothesis that *W. somnifera* has been shown to increase female sexual function in healthy women, indicating its potential as a treatment for sexual dysfunctions [62].

With regard to aphrodisiac effects on men, Chauhan et al (2022) carried a randomized, double-blind, placebo-controlled study using the plant extract in a dose of 300 mg orally. The study involved 50 men aged between 21 and 45 years who reported low sexual desire. They applied the Male Sexual Function Questionnaire (DISF-M) and the SF-36 quality of life questionnaire and measured serum testosterone levels and serum prolactin levels, being all parameters assessed before and after the intervention. The results showed that there was an increase in the total DISF-M scores, indicating an improvement in sexual function compared to placebo. In addition, serum testosterone levels increased significantly in the group treated with Ashwagandha. However, prolactin levels did not change significantly in both groups after the intervention. Accordingly, *W. somnifera* is associated with significant improvement in the subjective perception of sexual well-being and increases testosterone levels in participants, reinforcing its potential as a treatment to improve also male sexual health [61].

2.4 Peruvian Maca and its popular uses

Lepidium meyenii Walp., commonly known as Peruvian Maca, is a plant belonging to the Brassicaceae (Cruciferae) family. It is traditionally endemic to the Central Andes, found in countries such as Peru, Bolivia, and northwestern Argentina [63]. It adapts well to these regions due to the significant presence of rocky formations, intense sun exposure, and strong winds. Its popular name, "Peruvian Maca," is closely linked to its geographic origin.

Morphologically, the plant is a tuber, meaning it grows underground and has a characteristic elongated appearance composed of the main root and hypocotyl, while

its low foliage spreads across the soil [64]. The hypocotyls vary in color from purple to yellow, with studies indicating that these color differences signify distinct therapeutic actions [65]. Yellow maca is the most cultivated in Peru and is known for boosting energy, improving concentration, and promoting synthesis [65]. Red maca, which accounts for 25% of the harvest, is rich in phytochemicals and is considered more beneficial for female and bone health [64] Black maca, representing 15% of the harvest, is particularly recommended for enhancing libido and promoting muscle mass gain [64].

Its flavor and aroma are characteristic, with some suggesting its taste similar to caramel when the roots are consumed cooked [66]. Ideally, the roots should be processed into powder and can be added to foods to enhance their nutritional value or for pharmacological purposes [66]

Its popular use has been done for at least 2000 years by the traditional peoples of the Andean region, being harvested at altitudes of 4000 to 4500 meters. Widely used as a nutritional supplement and for its pharmacological properties, the uses of *L. meyenii* are diverse. Traditionally, it is used by indigenous cultures as an aphrodisiac to increase fertility in both men and women [64,67]. Additionally, maca possesses neuroprotective, antioxidant effects, and improves memory, fatigue, and delay aging, among others [66]

Currently, its use is no longer restricted to the Andean regions and is distributed worldwide, with the pharmaceutical industry being the largest consumer of maca roots, commercializing it primarily as a supplement for libido enhancement and improved physical performance [66]

2.4.1 Chemical composition

The chemical composition of Peruvian Maca can be divided into two groups: primary and secondary compounds. Gloria Vasquez conducted the phytochemical identification of the plant in 1968, being the first to categorize the chemical components of *L. meyenii* [68].

The roots are the main focus of *L. meyenii*, being the most used for pharmacological purposes, containing over 80% water, as well as starch and amylopectin [69]. For non-starchy polysaccharides, galacturonic acid, glucose, galactose, and arabinose have been identified [70]. Regarding proteins, valine was found in greater abundance (65 mg/g of protein) [71]. Its composition depends on different regions, waters, soils, handling, and harvesting, as well as its color [72].

L. meyenii is rich in alkaloids, including macamides, amide alkaloids, macaridines, and carbolic and imidazole alkaloids [72]. Studies hypothesize that macamides are the bioactive compound responsible for the pharmacological action. Macamides are secondary amides of the maca root, formed by benzylamine and fatty acids (Figure 4) [73]. They are considered typical lipid-soluble markers, facilitating hormone secretion stimulation and associating this characteristic with pharmacological action, such as improved sexual performance and neuroprotective activities. The effects of macamides as an anti-fatigue agent was investigated in mice, showing favorable results, suggesting that they are responsible for its pharmacological effect [73].

Wang and Zhu (2019) identified that polyphenols are responsible for increasing sperm production and daily sperm count [74], as well as essential amino acids, such as arginine. Thus, it can be inferred that the main compounds

responsible for the pharmacological action of Peruvian maca are arginine and macamides, as described so far.

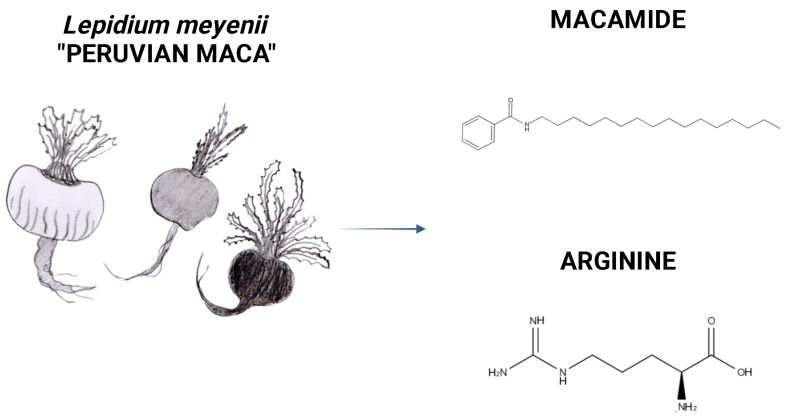


Figure 4. Representation of the plant *Lepidium meyenii* and structures of Macamides and arginine, the main chemical compounds responsible for known pharmacological action. Molecules were obtained using Molview (https://molview.org/)

2.4.2 Potential mechanism of action

As for the plant's mechanism of action, this is not yet well elucidated and understood. Botanically, *L. meyenii* is considered an adaptogenic plant, which is a characteristic that is capable of modulating hormones and the immune system [71]. Plants with this characteristic have the hypothalamic-pituitary-adrenal axis as their mechanism. However, there are many gaps regarding the androgenic mechanism, being generalized as acting through hormonal and endocrine effects due to the characteristics of its active compounds such as macamide which, due to its lipophilic chemical characteristics [73] and influences hormone production and secretion, thus being able to act on hormones such as testosterone, thus acting on sexual function and extending to physical performance.

2.4.3 Clinical and *in vivo* studies

Regarding pharmacological effects and clinical study with Shin et al (2023) , maca consumption has been associated with positive effects on sexual health for many years, initially in the Andes and now worldwide, being consumed with the aim of increasing sexual libido, fertility, and spermatogenesis [75].

Studies have investigated the effects of *L. meyenii* on sexual function, such as Shin et al. (2023) who observed the effects of Maca in patients with hypogonadism. In a randomized, double-blind, placebo-controlled study, 80 men aged ≥ 40 years were followed for 12 weeks. Efficacy was analyzed by scores on the Aging Males symptoms scale (AMS), Androgen Deficiency in Aging Men (ADAM), International Index of Erectile Function (IIEF) and International Prostate Symptom Score (IPSS) questionnaires, serum levels of total testosterone, free testosterone, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol

and triglycerides. After the first 4 weeks of treatment, improvement was seen in the AMS and ADAM scores in both groups. However, after 12 weeks the improvement in the group treated with Maca was significantly superior to placebo.The results show that maca could be investigated as a substitute for TRT for improving symptoms, as it has no adverse effects, is safe for prostate cancer patients and could be a promising alternative, but further studies are needed. [76]

Li et al. (2017) analyzed the effects of *L. meyenii* in relation to anti-fatigue effects. The plant extract was administered to male mice, followed by a swimming test [77]. During swimming, various biomarkers were determined, such as glutathione peroxidase, lactate dehydrogenase, creatine kinase, blood urea nitrogen, malondialdehyde, lactic acid, blood lactate, among others, and hepatic glycogen. Maca root powder at a dose of 400 mg/kg for 30 days prolonged swimming duration, increased hepatic glycogen content, and decreased lactic acid in the blood of male Kunming mice [77].

3. Discussion

Analyzing the data presented in this review, we found several similarities among the four plants discussed, *E. longifolia*, *T. terrestris, W. somnifera*, and *L. meyenii*. These plants have been traditionally used for hundreds of years and are known for their aphrodisiac effects. However, none of them have fully elucidated mechanisms of action, raising the hypothesis that they may involve multiple active compounds acting through different endocrine pathways, regulating and stimulating the production of hormones such as androgens. Another common point seems to be the hypothalamic-pituitary-gonadal (HPG) axis, as some studies have found the presence of compounds in Leydig and Sertoli cells, as well as increased testosterone levels.

For *E. longifolia*, studies such as those by Ang and Sim and Ang and Ngai discuss the function and relationship of the hypothalamic-pituitary-gonadal axis, relating it to increased libido and sexual performance in animal and human models [21,27]. In the case of *T. terrestris*, it has shown potential to increase testosterone levels and improve erectile function and libido, which is consistent with the synthesis and production pathways of testosterone, such as the gonadotropin-releasing hormone (GnRH) also present in the hypothalamic-pituitary-gonadal axis [35,44,45]. *W. somnifera* acts on Leydig and Sertoli cells, also influencing the hypothalamic-pituitary-adrenal axis [48].

The mechanism of *L. meyenii,* on the other hand, presents many gaps, and it is not yet clear which pathways it acts upon. Its effects related to increased libido, fertility, and spermatogenesis appear to be associated with the endocrine system, and its chemical compounds facilitate the production and secretion of hormones such as testosterone and estradiol [74,78]. Overall, these plants seem to improve sexual health and performance by acting on hormone production and secretion through hormonal regulation and stimulation.

Analyzing the positive effects of experimental studies conducted with these plants (Table 1) and knowing the relationship between regular physical exercise and the production of androgenic hormones such as testosterone, we can hypothesize that the consumption of dietary supplements based on the mentioned plants may be beneficial for improving physical activity at correct doses. But, more research is needed to fully understand their mechanisms of action.

Bearing in mind that the purpose of using these plants on the market today is as hormone modulators, it is important to think about the bigger picture in relation to the safety of the user, who is not suffering from hypogonadism, with the ideal basal levels of the hormones in question, thus potentially triggering problems due to their increased secretion. Bearing in mind that it is sold as a supplement and not as a medicine, the monitoring of adverse effects may be less strict, which could lead to long-term adverse effects that are difficult to detect.

Table 1: Analysis of the efficacy in different *in vivo* and clinical trials of *Eurycoma longifolia*, *Tribulus terrestris*, *Withania somnifera* and *Lipidium meyenii* for improving sexual and physical performance

Herbal drug	Dose (mg/kg); route of administration; treatment time	Experimental group	Outcome of treated group	Study type	Reference
Eurycoma longifolia	200, 400 and 800 mg/kg 2x day orally (10 days)	adult males rats (20 rats group)	enhanced sexual function	*In vivo*	Ang and Sim 1997
	500 mg/kg 1x day orally (4 weeks)	adult males rats (20 rats group)	increased libido		Ang and Ngai 2001
	200,400 and 800 mg/kg 1x day orally (12 weeks)	adults male rats (6 rats group)	increased in density the levator ani muscle and sexual function		Ang and Cheang 2001
	8 mg/kg 1x day orally (15 days)	adult males rats (6 rats group)	lower estrogen levels, increasing spermatogenesis and sperm counts		Wahab et al. 2010
Tribulus terrestris	2.5, 5 and 10 mg/kg 1x day (8 weeks)	adult males rabbits (6 rabbits group)	increased erection time and nitric oxide	*In vivo*	Adaikan et al. 2000
	5 mg/kg orally (8 weeks) 1x day	male rats (8 rats group)	improvement of sexual parameters		Gauthaman et al. 2002
	50-100 mg/kg (28 days) *	male rats (6 rats group)	increased serum testosterone levels		Singh et al 2012

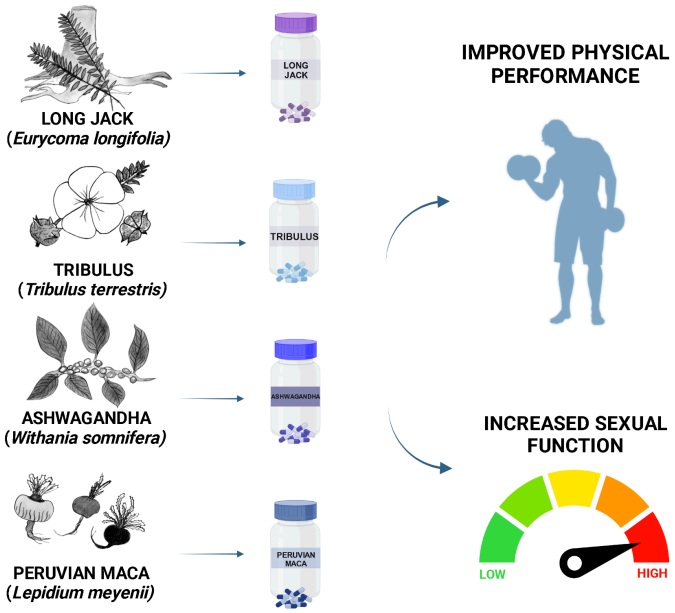
	500 mg 3x day (6 months)	males aged 18- 65 years (180 men)	increased libido and sexual function	Clinical Trial	Kamenov et al 2017
Withania somnifera	300 mg 2x day (8 weeks)	women 21-50 years (50 female)	increased sexual function	Clinical trial	Dongre et al 2015
	300 mg 2x day (8 weeks)	men 21-45 years (50 males)	increased testosterone levels and sexual function	Clinical trial	Chauhan et al. 2022
Lepidium meyenii	1000mg (12 weeks) 6x days	men ≥ 40 years (80 males)	improved function sexual in patients with hypogonadism	Clinical trial	Shin et al 2023
	400m/kg	male rats	anti-fatigue effects	*In vivo*	Li et al 2017

4. Conclusion

This review compiled literature on the potential of natural components already known as aphrodisiacs to potentially enhance testosterone levels, linking increased libido with physical performance. The use of these compounds has been widespread for centuries, and currently, they are gaining traction in the commercial market, moving beyond just traditional medicine.

However, upon reviewing the current literature, we identified significant gaps in the knowledge, particularly regarding physical exercise. For instance, *Tribulus* is primarily marketed in Brazil with promises of improved physical performance, but its mechanisms of action are not well elucidated, similar to other compounds that raise many assumptions about their mechanisms.

In summary, although these natural compounds offer potential for improving sexual health, as advocated by both Western and Eastern traditional medicine, there is a need for further investigation to fill these knowledge gaps and clarify their use for the general population.



Graphical abstract: General outcomes of *Eurycoma longifolia* (Long Jack), *Tribulus terrestris* (Tribulus), *Withania somnifera* (Ashwagandha) and *Lipidium meyenii* (Peruvian Maca) linked to an action of physical performance and sexual function. Illustration created partially with BioRender (https://app.biorender.com/).

References

[1] F. C. Bull, S. S. Al-Ansari, S. Biddle, K. Borodulin, M. P. Buman, G. Cardon, C. Carty, J.-P. Chaput, S. Chastin, R. Chou, P. C. Dempsey, L. DiPietro, U. Ekelund, J. Firth, C. M. Friedenreich, L. Garcia, M. Gichu, R. Jago, P. T. Katzmarzyk, E. Lambert, M. Leitzmann, K. Milton, F. B. Ortega, C. Ranasinghe, E. Stamatakis, A. Tiedemann, R. P. Troiano, H. P. van der Ploeg, V. Wari, J. F. Willumsen, *Br. J. Sports Med.* **2020**, *54*, 1451–1462.

[2] A. L. Miller, *Altern. Med. Rev.* **1998**, *3*, 422–431.

[3] R. Gautam, S. M. Jachak, *Med. Res. Rev.* **2009**, *29*, 767–820.

[4] M. Schnekenburger, M. Dicato, M. Diederich, *Biotechnol. Adv.* **2014**, *32*, 1123–1132.

[5] M. Saleem, M. Nazir, M. S. Ali, H. Hussain, Y. S. Lee, N. Riaz, A. Jabbar, *Nat. Prod. Rep.* **2010**, *27*, 238–254.

[6] S. Kotta, S. H. Ansari, J. Ali, *Pharmacogn. Rev.* **2013**, *7*, 1–10.

[7] R. B. van Breemen, H. H. Fong, N. R. Farnsworth, *Am. J. Clin. Nutr.* **2008**, *87*, 509S–13S.

[8] P. L. Schiff Jr, V. S. Srinivasan, G. I. Giancaspro, D. B. Roll, J. Salguero, M. H. M. Sharaf, *J. Nat. Prod.* **2006**, *69*, 464–472.

[9] H. O. Santos, S. Howell, F. J. Teixeira, *J. Ethnopharmacol.* **2019**, *235*, 392–405.

[10] C. G. Clemesha, H. Thaker, M. K. Samplaski, *World J. Mens Health* **2020**, *38*, 115–122.

[11] FDA, “Questions and Answers on Dietary Supplements,” can be found under https://www.fda.gov/food/information-consumers-using-dietary-supplements/questions-and-answers-dietary-supplements, **2024**.

[12] J. L. Vingren, W. J. Kraemer, N. A. Ratamess, J. M. Anderson, J. S. Volek, C. M. Maresh, *Sports Med.* **2010**, *40*, 1037–1053.

[13] P. Dandona, M. T. Rosenberg, *Int. J. Clin. Pract.* **2010**, *64*, 682–696.

[14] A. Thirumalai, B. D. Anawalt, *Rev. Endocr. Metab. Disord.* **2022**, *23*, 1305–1322.

[15] T. Sen, S. K. Samanta, *Adv. Biochem. Eng. Biotechnol.* **2015**, *147*, 59–110.

[16] A. Y. Duraz, S. A. Khan, *Oman Med. J.* **2011**, *26*, 451–453.

[17] S. U. Rehman, K. Choe, H. H. Yoo, *Molecules* **2016**, *21*, 331.

[18] “Malaysian Herbal Monograph,” can be found under https://globinmed.com/medicinal_herbs/eurycoma-longifolia-jack-update-050422/, **2022**.

[19] K. L. Chan, M. J. O’Neill, J. D. Phillipson, D. C. Warhurst, *Planta Med.* **1986**, 105–107.

[20] Y. Zakaria, A. Rahmat, A. H. L. Pihie, N. R. Abdullah, P. J. Houghton, *Cancer Cell Int.* **2009**, *9*, 16.

[21] H. H. Ang, M. K. Sim, *Exp. Anim.* **1997**, *46*, 287–290.

[22] M. A. Farag, A. O. Ajayi, M. Taleb, K. Wang, I. M. Ayoub, *ACS Omega* **2023**, *8*, 1838–1850.

[23] P.-C. Kuo, A. G. Damu, K.-H. Lee, T.-S. Wu, *Bioorg. Med. Chem.* **2004**, *12*, 537–544.

[24] R. Bhat, A. A. Karim, *Fitoterapia* **2010**, *81*, 669–679.

[25] B.-S. Low, P. K. Das, K.-L. Chan, *J. Ethnopharmacol.* **2013**, *145*, 706–714.

[26] L. S. Chua, N. A. M. Amin, J. C. H. Neo, T. H. Lee, C. T. Lee, M. R. Sarmidi, R. A. Aziz, *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **2011**, *879*, 3909–3919.

[27] H. H. Ang, T. H. Ngai, *Fundam. Clin. Pharmacol.* **2001**, *15*, 265–268.

[28] H. H. Ang, H. S. Cheang, *Arch. Pharm. Res.* **2001**, *24*, 437–440.

[29] V. Rochira, L. Zirilli, A. D. Genazzani, A. Balestrieri, C. Aranda, B. Fabre, P. Antunez, C. Diazzi, C. Carani, L. Maffei, *Eur. J. Endocrinol.* **2006**, *155*, 513–522.

[30] N. A. Wahab, N. M. Mokhtar, W. N. H. A. Halim, S. Das, *Clinics* **2010**, *65*, 93–98.

[31] P. G. Adaikan, K. Gauthaman, R. N. V. Prasad, *Aging Male* **2001**, *4*, 163–169.

[32] I. Kostova, D. Dinchev, *Phytochem. Rev.* **2005**, *4*, 111–137.

[33] D. Dinchev, B. Janda, L. Evstatieva, W. Oleszek, M. R. Aslani, I. Kostova, *Phytochemistry* **2008**, *69*, 176–186.

[34] S. Chhatre, T. Nesari, G. Somani, D. Kanchan, S. Sathaye, *Pharmacogn. Rev.* **2014**, *8*, 45–51.

[35] P. G. Adaikan, K. Gauthaman, R. N. Prasad, S. C. Ng, *Ann. Acad. Med. Singapore* **2000**,

29, 22–26.
[36] I. Kostova, D. Dinchev, G. H. Rentsch, V. Dimitrov, A. Ivanova, *Z. Naturforsch. C* **2002**, *57*, 33–38.
[37] A. Pokrywka, Z. Obmiński, J. Malczewska-Lenczowska, Z. Fijałek, E. Turek-Lepa, R. Grucza, *J. Hum. Kinet.* **2014**, *41*, 99–105.
[38] H. Usman, F. I. Abdulrahman, A. H. Ladan, *Res. J. Bio. Sci. Medwell Journals* **2007**, *2*, 244–247.
[39] R. Ștefănescu, A. Tero-Vescan, A. Negroiu, E. Aurică, C.-E. Vari, *Biomolecules* **2020**, *10*, DOI 10.3390/biom10050752.
[40] I. Pharmacopoeia, *Government of India* **1996**, *2*, 350.
[41] J. Do, S. Choi, J. Choi, J. S. Hyun, *Korean J. Urol.* **2013**, *54*, 183–188.
[42] V. K. Neychev, V. I. Mitev, *J. Ethnopharmacol.* **2005**, *101*, 319–323.
[43] S. Singh, V. Nair, Y. K. Gupta, *J. Pharmacol. Pharmacother.* **2012**, *3*, 43–47.
[44] K. Gauthaman, P. G. Adaikan, R. N. V. Prasad, *Life Sci.* **2002**, *71*, 1385–1396.
[45] Z. Kamenov, S. Fileva, K. Kalinov, E. A. Jannini, *Maturitas* **2017**, *99*, 20–26.
[46] N. J. Dar, A. Hamid, M. Ahmad, *Cell. Mol. Life Sci.* **2015**, *72*, 4445–4460.
[47] L. C. Mishra, B. B. Singh, S. Dagenais, *Altern. Med. Rev.* **2000**, *5*, 334–346.
[48] S. Paul, S. Chakraborty, U. Anand, S. Dey, S. Nandy, M. Ghorai, S. C. Saha, M. T. Patil, R. Kandimalla, J. Proćków, A. Dey, *Biomed. Pharmacother.* **2021**, *143*, 112175.
[49] N. Singh, M. Bhalla, P. de Jager, M. Gilca, *Afr. J. Tradit. Complement. Altern. Med.* **2011**, *8*, 208–213.
[50] P. Pawar, S. Gilda, S. Sharma, S. Jagtap, A. Paradkar, K. Mahadik, P. Ranjekar, A. Harsulkar, *BMC Complement. Altern. Med.* **2011**, *11*, 34.
[51] G. Singh, P. Kumar, *Indian J. Pharm. Sci.* **2011**, *73*, 473–478.
[52] V. N. Sumantran, A. Kulkarni, S. Boddul, T. Chinchwade, S. J. Koppikar, A. Harsulkar, B. Patwardhan, A. Chopra, U. V. Wagh, *J. Biosci.* **2007**, *32*, 299–307.
[53] K. Vaishnavi, N. Saxena, N. Shah, R. Singh, K. Manjunath, M. Uthayakumar, S. P. Kanaujia, S. C. Kaul, K. Sekar, R. Wadhwa, *PLoS One* **2012**, *7*, e44419.
[54] D. A. Bonilla, Y. Moreno, C. Gho, J. L. Petro, A. Odriozola-Martínez, R. B. Kreider, *J Funct Morphol Kinesiol* **2021**, *6*, DOI 10.3390/jfmk6010020.
[55] R. Archana, A. Namasivayam, *J. Ethnopharmacol.* **1999**, *64*, 91–93.
[56] J. Zhao, N. Nakamura, M. Hattori, T. Kuboyama, C. Tohda, K. Komatsu, *Chem. Pharm. Bull.* **2002**, *50*, 760–765.
[57] D. Lavie, I. Kirson, E. Glotter, *Isr. J. Chem.* **1968**, *6*, 671–678.
[58] N. P. Visavadiya, A. V. R. L. Narasimhacharya, *Phytomedicine* **2007**, *14*, 136–142.
[59] R. M. Sharpe, *J. Endocrinol.* **1993**, *136*, 357–360.
[60] S. Dongre, *Trupti Hospital & Santati Fertility Center, Mumbai* **n.d.**
[61] S. Chauhan, M. K. Srivastava, A. K. Pathak, *Health Sci Rep* **2022**, *5*, e741.
[62] S. Dongre, D. Langade, S. Bhattacharyya, *Biomed Res. Int.* **2015**, *2015*, 284154.
[63] C. Ochoa, *Econ. Bot.* **2001**, *55*, 344–345.
[64] J. León, *Econ. Bot.* **1964**, *18*, 122–127.
[65] D. M. Minich, K. Ross, J. Frame, M. Fahoum, W. Warner, H. O. Meissner, *Nutrients* **2024**, *16*, DOI 10.3390/nu16040530.
[66] N. da Silva Leitão Peres, L. Cabrera Parra Bortoluzzi, L. L. Medeiros Marques, M. Formigoni, R. H. B. Fuchs, A. A. Droval, F. A. Reitz Cardoso, *Food Funct.* **2020**, *11*, 83–92.
[67] M. Hermann, *Andean Roots and Tubers: Ahipa, Arracacha, Maca and Yacon*, International Potato Center, **1997**.
[68] L. Chen, Z. Hu, Z. Wu, G. Wu, L. Ma, C. Zhang, Y. Huang, *Compos. Part A Appl. Sci. Manuf.* **2017**, *96*, 1–8.
[69] L. G. Valerio Jr, G. F. Gonzales, *Toxicol. Rev.* **2005**, *24*, 11–35.
[70] L. Zhang, X. Dou, W. Kong, C. Liu, X. Han, M. Yang, *J. Chromatogr. A* **2017**, *1483*, 56–63.
[71] G. F. Gonzales, *Evid. Based. Complement. Alternat. Med.* **2012**, *2012*, 193496.
[72] S. Wang, F. Zhu, *Food Chem.* **2019**, *288*, 422–443.

[73] Q. Yang, W. Jin, X. Lv, P. Dai, Y. Ao, M. Wu, W. Deng, L. Yu, *Pharm. Biol.* **2016**, *54*, 827–834.
[74] G. F. Gonzales, A. Ruiz, C. Gonzales, L. Villegas, A. Cordova, *Asian J. Androl.* **2001**, *3*, 231–233.
[75] M. J. D. do A. L. Balick, *Alternative Therapies in Health and MedicineVisualizar detalhes do artigo; Aliso Viejo volume* **2002**, *8*, 96–98.
[76] D. Shin, S. H. Jeon, J. Piao, H. J. Park, W. J. Tian, D. G. Moon, S. T. Ahn, K.-H. Jeon, G. Q. Zhu, I. Park, H.-J. Park, W. J. Bae, H. J. Cho, S.-H. Hong, S. W. Kim, *World J. Mens Health* **2023**, *41*, 692–700.
[77] J. Li, Q. Sun, Q. Meng, L. Wang, W. Xiong, L. Zhang, *Int. J. Biol. Macromol.* **2017**, *95*, 1305–1311.
[78] B. L. Zheng, K. He, C. H. Kim, L. Rogers, Y. Shao, Z. Y. Huang, Y. Lu, S. J. Yan, L. C. Qien, Q. Y. Zheng, *Urology* **2000**, *55*, 598–602.