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Profile of prescriptions for anabolic herbal medicines marketed by a magistral pharmacy in Rio de Janeiro

Perfil das prescrições de fitoterápicos anabolizantes comercializados por uma farmácia magistral no Rio de Janeiro

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ABSTRACT

Introduction: Since antiquity, humans have used plants for various purposes, including improving physical performance. However, in recent years, the search for herbal medicines aimed at mimicking the anabolic effect, with lower health risks and without being detected in doping control, has sparked the interest of athletes and gym users. **Objective:** To evaluate which herbal drugs with possible androgenic activity are prescribed as magistral formulations in the city of Rio de Janeiro. **Method:** Data from 10,276 prescriptions recorded in the database of a network of compounding pharmacies located in the city of Rio de Janeiro between January and December 2020 were collected and analyzed. The prescribed and dispensed formulations contained *Ajuga turkestanica, Cyanotis vaga, Eurycoma longifolia, Lepidium meyenii, Mucuna pruriens, Tribulus terrestris, Trigonella foenum-graecum,* and *Withania somnifera*. **Results:** Most prescriptions (57.0%) were for women, prescribed by specialists in orthomolecular medicine (38.0%), and only 4.0% of prescriptions were prescribed by nutritionists. Regarding the types of medications, 8,116 prescriptions (79.0%) were formulations of combinations of one or more anabolic herbal drugs with pharmaceuticals. *M. pruriens* was the most prescribed herbal drug (29.0%), with or without combination. **Conclusions:** Most of the prescribed plants still do not have proven efficacy and safety regarding anabolic action; therefore more clinical studies are necessary to determine the possible drug interactions and adverse effects of these herbal drugs.

KEYWORDS: Phytotherapeutic Drugs; Doping; Anabolic Agents; Testosterone; Ergogenic Effect

RESUMO

Introdução: Desde a antiguidade, o homem utiliza as plantas para diferentes finalidades, inclusive para melhorar o desempenho físico. Porém, em anos recentes, a busca por fitoterápicos destinados a mimetizar o efeito anabolizante, com menor risco para a saúde e sem ser detectado no controle *antidoping* vem despertando o interesse de atletas e de usuários de academias. **Objetivo:** Avaliar quais são as drogas vegetais com possível atividade androgênica prescritas magistralmente na cidade do Rio de Janeiro. **Método:** Dados de 10.276 prescrições registradas no banco de dados de uma rede de farmácias de manipulação, localizada na cidade do Rio de Janeiro, entre o período de janeiro a dezembro de 2020, foram coletados e analisados. As formulações prescritas e aviadas continham *Ajuga turkestanica*, *Cyanotis vaga*, *Eurycoma longifolia*, *Lepidium meyenii*, *Mucuna pruriens*, *Tribulus terrestris*, *Trigonella foenum-graecum* e *Withania somnifera*. **Resultados:** A maioria das prescrições (57,0%) foi destinada a mulheres, receitadas por médicos especialistas em medicina ortomolecular (38,0%) e apenas 4,0% das receitas foram prescritas por nutricionistas. Quanto aos tipos de medicamentos, 8.116 prescrições (79,0%) eram formulações de associações de uma ou mais drogas vegetais anabolizantes com fármacos. *M. pruriens* foi a droga vegetal mais prescrita (29,0%), com

ou sem associação. **Conclusões:** A maioria das plantas prescritas ainda não possui eficácia e segurança comprovadas quanto à ação anabolizante e, por isso, mais estudos clínicos são necessários, além da determinação das possíveis interações medicamentosas e efeitos adversos dessas drogas vegetais.

PALAVRAS-CHAVE: Medicamento Fitoterápico; *Doping*; Anabolizantes; Testosterona; Efeito Ergogênico

INTRODUCTION

Brazil is currently considered the world's largest market for compounding pharmacies, with more than 8,100 units. According to the National Association of Magistral Pharmacies (ANFARMAG), there has been an 11.8% increase in the number of these establishments in the country over the last 5 years[1]. In the natural products segment, compounding pharmacies stand out for filling prescriptions for herbal medicines and/or their associations with drugs. The prescription of herbal medicines should be done conscientiously by legally qualified professionals such as doctors, veterinary surgeons, dental surgeons[2], pharmacists[3], and nutritionists[4].

The prescription of herbal medicines is expanding due to the growing interest in natural therapies[5], the action of the pharmaceutical marketing sector and the sales reps of the magistral pharmacy, in which prescribers receive information about the active ingredients and new pharmaceutical forms.

In 2016, the Brazilian National Health Surveillance Agency (Anvisa)[6] published a document to guide the prescription and use of herbal medicines in Brazil, the Herbal Medicines Memento (*Memento Fitoterápico da Farmacopeia Brasileira*). It includes monographs with technical-scientific evidence on botanical identification, therapeutic indications, contraindications, precautions for use, adverse effects, drug interactions, pharmaceutical forms, routes of administration, dosage, the main chemical classes, and information on the safety and efficacy of medicinal plants presented in the form of herbal medicines[7]. However, this guide does not cover all the plant drugs that are being prescribed in herbal formulations and manipulated in pharmacies in the country.

The use of medicinal plants is a practice that has existed since the beginning of humanity and knowledge about them has been passed down from generation to generation. Today they are easily found in fairs, markets, health food stores and cultivated in backyards, and the fact that they are of natural origin can lead to the understanding that their use is unrestricted and without adverse effects[7,8]. Students, artists, intellectuals, the military, and, above all, sportspeople have been searching for new chemical substances capable of improving performance, whether physical or intellectual[9,10].

The use of herbal medicines as a supplement to improve sports performance, promote muscle hypertrophy, increase serum testosterone levels, and achieve aesthetic goals has been widespread in both therapeutic practice and popular culture. However, despite the prescription of various medicinal plants for these purposes by various health professionals, including doctors and nutritionists, clinical evidence proving their efficacy and safety is still limited. Among the main plants used to improve physical performance and promote muscle hypertrophy are: *Tribulus terrestris*, *Mucuna pruriens*, *Lepidium meyenii*, *Coleus forskohlii*, *Eurycoma longifolia*[11,12]. In addition, isolated substances of natural origin, such as caffeine (origin: *Coffea* sp.) and ephedrine (origin: *Ephedra sinensis*), have long been used by athletes as sports supplements[13], and are monitored by the anti-doping program of the World Anti-Doping Agency (WADA). Caffeine is considered non-prohibited for use among athletes, while ephedrine is considered a stimulant and prohibited when its concentration in urine is greater than 10 µg/ml[14].

The purpose of this study was to identify and analyze the prescriptions for herbal medicines containing plant drugs with possible androgenic activity, handled by a chain of magistral pharmacies in the city of Rio de Janeiro, RJ.

METHOD

This is a quantitative, exploratory, cross-sectional study using documentary and bibliographic research. It began with a request for authorization to access the prescription database of a chain of magistral pharmacies located in the city of Rio de Janeiro. The research did not require the approval of a research ethics committee, as it guaranteed the confidentiality and anonymity of any information collected that could identify the people mentioned in the prescriptions.

The parameters analyzed in the manipulated herbal prescriptions from January to December 2020 were identification of anabolic plant drugs (APD), type of prescriptions, quantity of APD per prescription, gender of clients, and profile of prescribers.

The bibliographic research was carried out in January 2022 by accessing the CAPES Periodicals Portal, in the PubMed, Web of Science, and ScienceDirect databases in the English language, using the following keywords: scientific name of the APD: *Ajuga turkestanica* (Rgl.) Brig, *Cyanotis vaga* (Lour.) Schult. f., *Eurycoma longifolia* Jack, *Lepidium meyenii* Walp., *Mucuna pruriens* (L.) DC., *Tribulus terrestris* L., *Trigonella foenum-graecum* L., *Withania somnifera* (L.) Dunal and/or *testosterone* or *anabolic* or *doping*. Duplicate articles that did not address the objective of this study were excluded. The research variables were analyzed in a descriptive and mathematical-statistical way, using absolute frequency and percentage from tables and graphs prepared in the Excel® program.

RESULTS AND DISCUSSION

Plant-based drugs

Analysis of each of the prescriptions containing at least one of the eight APDs showed the presence of 13,883 APD units distributed among the 10,276 prescriptions issued in 2020 by a chain of compounding pharmacies in the municipality of Rio de Janeiro (Table 1). *M. pruriens* was the most prescribed plant drug in the prescriptions analyzed, totaling 4,047 (29.0%), followed by *W. somnifera* (2,901, 21.0%), *T. terrestris* (2,642, 19.0%), *L. meyenii* (2,097, 15.0%), *E. longifolia* (1,251, 9.0%), *A. turkestanica* (618, 4.0%), *T. foenum-graecum* (202, 2.0%), and with the lowest number of prescriptions handled, *C. vaga* (125, 1.0%).

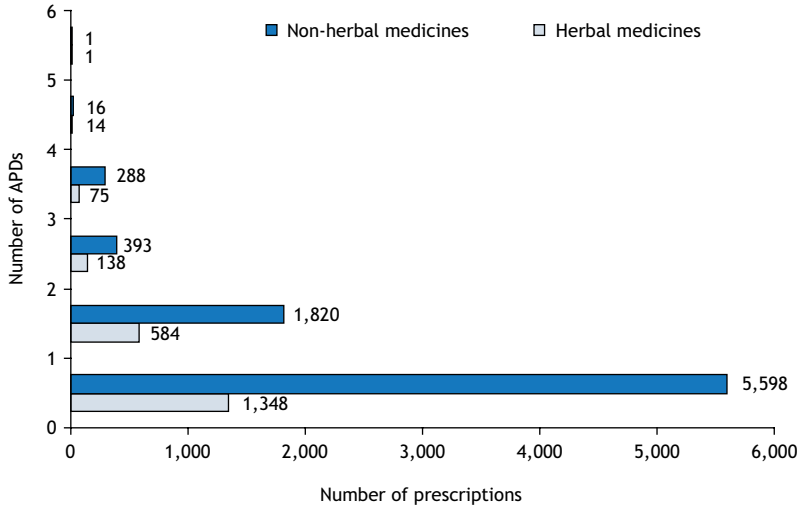
Types of medication

It can be seen that approximately 80.0% (8,116) of the prescriptions were for non-herbal prescription formulations (APD and addition of active ingredients), such as vitamins, minerals, amino acids, or drugs, possibly to enhance the performance of physical activities and gain muscle mass. While only 21.0% (2,160) of the total number of prescriptions were made exclusively with APDs, called magistral herbal medicines. Of these, 62.0% (1,348) had a single APD, followed by 27.0% (584) with two APDs and one prescription with a combination of six APDs. As for the non-herbal prescriptions, the same decreasing profile of formulations with an association of APDs with other active ingredients can be seen (Figure 1).

Table 1. Correlation between prescribers and APDs present in prescriptions in 2020 by a chain of compounding pharmacies in the municipality of Rio de Janeiro, RJ.

Prescriber	Anabolic plant drugs								Total	
	AT	CV	EL	LM	MP	TF	TT	WS	N	%
EG	48	16	173	381	723	19	396	379	2,135	16.0
EC	201	35	150	481	491	68	920	406	2,752	20.0
HM	1	1	34	41	261	7	20	122	487	3.5
MD	3	10	102	91	299	7	71	137	720	5.0
NC	51	7	74	132	60	15	141	150	630	4.5
NT	69	35	297	261	515	42	217	557	1,993	14.0
OM	245	21	421	710	1,698	44	877	1,150	5,166	37.0
Total N	618	125	1,251	2,097	4,047	202	2,642	2,901	13,883	100.0
%	4	1	9	15	29	2	19	21	-	100.0

Source: Prepared by the authors, 2023.
AT: *A. turkestanica*; CV: *C. vaga*; EL: *E. longfolia*; LM: *L. meyenii)*; MP: *M. pruriens*; TF: *T. foenum-graecum*; TT: *T. terrestris*; WS: *W. somnifera*; EG: Slimming; EC: Endocrinologist; HM: Muscle hypertrophy; MD: Sports medicine; NC: Nutritionist; NT: Nutrologist; OM: Orthomolecular.



Source: Prepared by the authors, 2023.

Figure 1. Correlation between the types of medicines (herbal and non-herbal) and the respective amounts of anabolic plant drugs (APD) present in the prescriptions filled in 2020 by a chain of compounding pharmacies in Rio de Janeiro, RJ.

The year 2020 was marked by the beginning of the coronavirus (COVID-19) pandemic, an infectious disease caused by the SARS-CoV-2 virus. The city of Rio de Janeiro was in lockdown from the second half of March until May, with outdoor sports reopening in June and gyms and sports centers in July. Possibly because of this, it can be seen that the month of January (1,129; 11%) was the month with the highest number of prescriptions prepared by the magistral pharmacy network, the period before the pandemic. During the lockdown, there was a drop of more than 50.0% in the number of prescriptions filled compared to January. Then, with the reopening of gyms and sports centers in June (815; 8%), July (844; 8%), August (920; 9%), and September (986; 10%), there was a gradual increase in the number of prescriptions filled (Figure 2).

Prescribers

Initially, the prescriptions containing APDs were divided by the professionals' areas of practice: into nutritionists and six types of medical specialties according to the magistral pharmacy system. The professionals who prescribed the most APDs were: orthomolecular doctors (5,166, 37.0%), followed by endocrinologists (2,752, 20.0%) and slimming clinicians (2,135, 16.0%) and nutritionists (1,993, 14.0%) (Table 1). No herbal prescriptions prescribed by pharmacists were found.

Since the publication of Federal Pharmacy Council Resolution No. 546 of July 21, 2011[15], pharmacists have been allowed to prescribe medicinal plants and herbal medicines without a prescription.

More recently, the publications of the Herbal Medicines Memento[6], the Brazilian Pharmacopoeia Phytotherapic Form[16] and Anvisa's Guidelines on the Use of Phytotherapics and Medicinal Plants[17] have been guiding health professionals on how to prescribe phytotherapics, the correct way to prepare them, indications, and restrictions on the use of various medicinal plants to be handled in pharmacies authorized by the National Health Surveillance System. According to Ramos et al.[18], pharmaceutical prescription is a growing experience in some developed countries with different health systems. Despite these advances, there are many challenges to consolidating this practice.

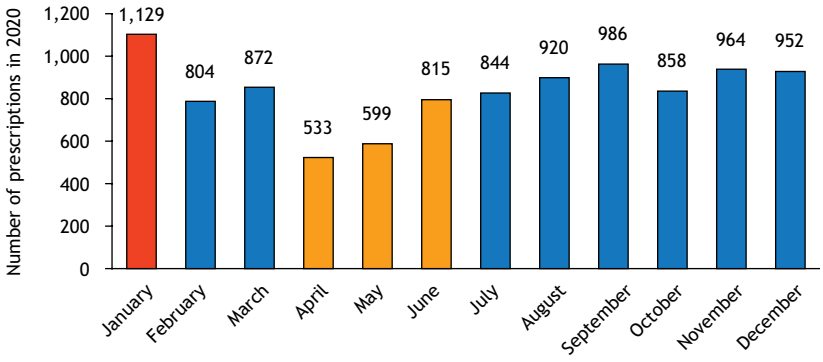
Patients/users

Regarding the sex of the patients, more prescriptions were written for women (5,894; 57.0%) than for men (4,382; 43.0%). According to data from the Brazilian Institute of Geography and Statistics[19], the female population in Rio de Janeiro is higher than the male population (52.14% and 48.86%, respectively), which may be one of the explanations for the result observed. Historically, men are considered to be strong beings who hardly ever get sick, which is why the demand for doctors' offices is predominantly female[20]. Women tend to seek out more medical specialties with personalized treatments, such as orthomolecular, in the search for a healthier life and prevention of aging. Possibly another factor contributing to the increase in the number of prescriptions for drugs for the female population is the policy of the marketing department of the magistral pharmacy, which makes visits to gynecologists with a specialty in orthomolecular medicine.

Female predominance is present in six of the seven specialties of prescriptions filled, with the exception of sports medicine, which showed a difference of only six units of prescriptions (Figure 3). In contrast to our results, the study by Maciel et al.[9] showed that, among sportspeople in gyms in Recife, Pernambuco, there is a high consumption of anabolic androgenic steroids, indicated by a physical educator or friend, administered in a pharmacy, the majority without a medical prescription and a predominance of adult users, aged between 26 and 35, with a university degree and male.

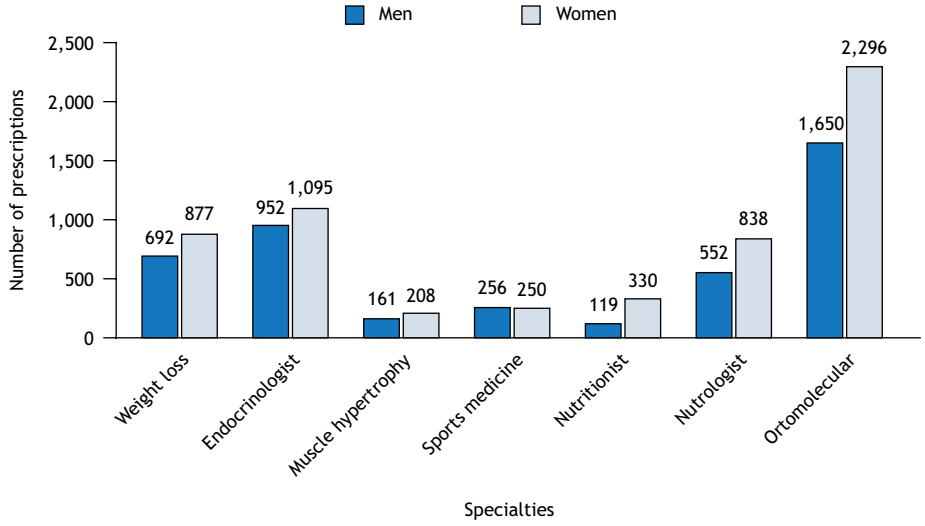
Scientific literature

The database search totaled 19,822 publications. The botanical species with the most scientific articles published was: *W. somnifera* (5,997; 30.0%), followed by *T. foenum-graecum* (5,263; 27.0%), *T. terrestris* (2,814; 14.0%), *M. pruriens* (2,440; 12.0%), *L. meyenii* (2,149; 11.0%), *E. longifolia* (1,046; 5.0%), and *A. turkestanica* (93; 1.0%), and the least studied plant



Source: Prepared by the authors, 2023.

Figure 2. Evolution of the number of prescriptions handled per month in 2020.



Source: Prepared by the authors, 2023.

Figure 3. Correlation between the number of prescriptions filled in 2020 by a pharmacy chain and the sex of the patients and the specialties of the APD prescribers.

species was *C. vaga* (Table 2). When adding the keywords *testosterone* or *doping* or *anabolic*, there was a significant reduction in the number of scientific articles published (Table 2). On the other hand, it reveals that there are other biological properties described for these APDs.

The overlapping of scientific articles in the three databases searched was not taken into account, nor were their articles excluded, as this is not a systematic review study.

Many health professionals prescribe medicinal plants that can have anabolic effects by increasing serum testosterone levels without reaching the doping threshold. Thus, the anabolic action of testosterone will provide increased physical performance and muscle mass gain among athletes and physical activity practitioners, which can be a great advantage in competitions.

A. turkestanica and *C. vaga* have phytoecdysteroids in their chemical composition (Figure 4), which are structural analogues of the insect moulting hormone ecdysone. *A. turkestanica* contains high levels of C-11 hydroxylated turquesterone, one of the most active ecdysteroids[21]. Ecdysteroids have several proven beneficial activities in mammals, but their hormonal effects still require further study. Their structures are somewhat similar to those of vertebrate steroid hormones, but there are structural differences between them. Despite these differences, these substances can serve as effective anabolic, hepatoprotective, immunoprotective, antioxidant, and hypoglycemic agents[22].

Lawrence et al.[23] observed that in a study of mice given an extract of *A. turkestanica* enriched in phytoecdysteroids, there was no change in body, muscle, or organ mass. In addition, protein synthesis signaling markers measured after 28 days or acutely remained unchanged in the skeletal muscle of ageing sedentary mice. In a 12-week randomized double-blind placebo-controlled study, phytoecdysteroid supplementation was found to improve skeletal muscle fitness in adults over 50 years of age. Muscle strength and muscle quality showed significant improvements, in addition, there was a significant decrease in fat mass and an increase in muscle mass[24].

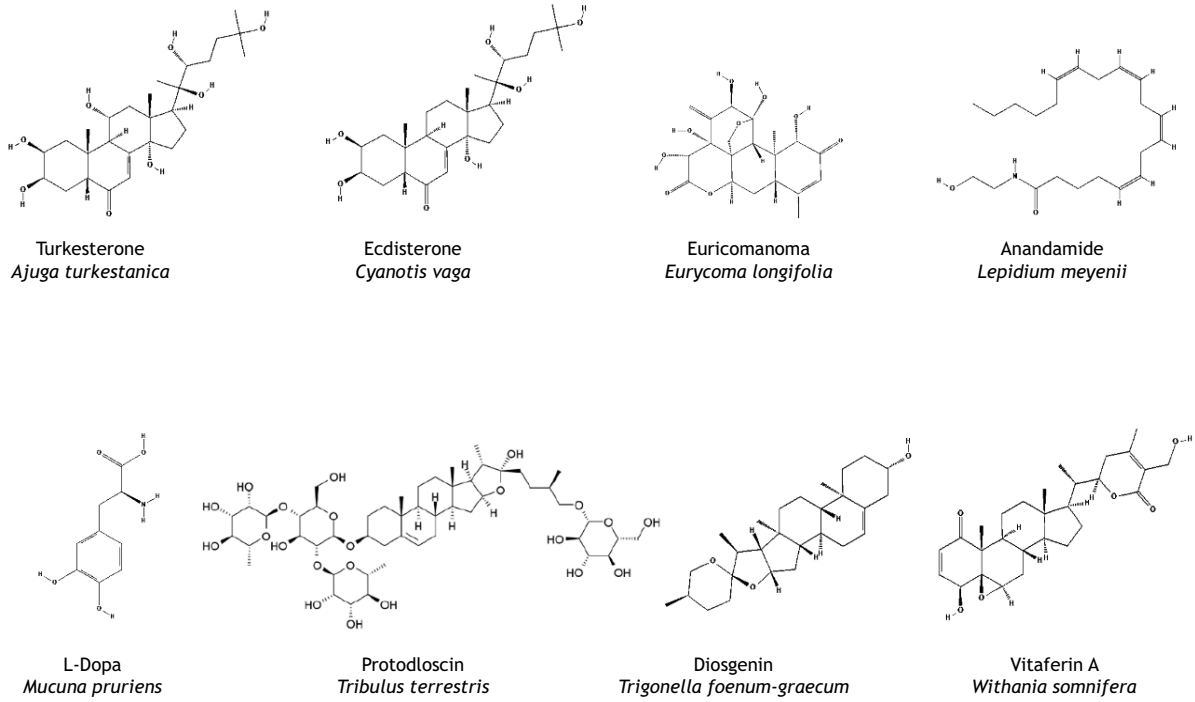
E. longifolia is a medicinal plant with possible aphrodisiac and tonic properties and anti-aging benefits. Extracts of the roots are used as food supplements, especially in the bodybuilding scene, due to their activity in "improving energy", resistance to stress, and especially in restoring hormonal balance, improving sports performance and weight loss. The active ingredients in long-jack are euripeptides derived from eurycomanone (Figure 4), classified as quassinoids. These metabolites are able to stimulate the release of free testosterone from its binding proteins and improve general hormonal profiles[25]. The increase in testosterone due to long-jack consumption is related to several mechanisms. In the hypothalamic-pituitary axis, it generates a greater stimulus for the release of luteinizing hormone (LH) by the pituitary gland and thus greater production and secretion of testosterone by the Leydig cells. In the process of testosterone synthesis, euripeptides act by potentiating the action of the CYP450c17 and e17 enzymes, consequently generating greater production of dehydroepiandrosterone (DHEA) and testosterone. In addition, these quassinoids act by inhibiting aromatase and decreasing the conversion of testosterone into estradiol or estrone[26]. In this randomized, double-blind, placebo-controlled study of 45 men with androgen deficiency of aging males (ADAM) over six months, 22 participants received a 200 mg supplement of *E. longifolia*. The main evidence from this study was: improvement in the five domains of sexual health (erectile function, sexual satisfaction, sexual desire, orgasmic function, and overall satisfaction), a 43% increase in testosterone levels and within the normal range for total testosterone (> 346 ng/dL). In contrast, the study by Chen et al.[27] showed that supplementation with 400 mg of *E. longifolia* for six weeks had

Table 2. Total number of scientific articles found in the PubMed, Science Direct, and Web of Science databases for APDs by scientific name plus keywords *testosterone*, *doping*, or *anabolic*.

Key words	PubMed	Science Direct	Web of Science	N	%
Ajuga turkestanica	13	38	42	**93**	**1.0**
Testosterone	0	4	0	**4**	
Doping	0	1	0	**1**	
Anabolic	11	10	5	**26**	
Cyanotis vaga	3	14	3	**20**	**<1.0**
Testosterone	0	2	0	**2**	
Doping	0	1	0	**1**	
Anabolic	1	3	0	**4**	
Eurycoma longifolia	280	359	407	**1.046**	**5.0**
Testosterone	38	85	56	**179**	
Doping	2	9	1	**12**	
Anabolic	83	16	5	**104**	
Lepidium meyenii	1,238	463	448	**2.149**	**11.0**
Testosterone	37	119	55	**211**	
Doping	3	10	0	**13**	
Anabolic	434	31	2	**467**	
Mucuna pruriens	301	1.191	948	**2.440**	**12.0**
Testosterone	12	94	17	**123**	
Doping	1	26	3	**30**	
Anabolic	122	41	0	**163**	
Tribulus terrestris	490	1.502	822	**2.814**	**14.0**
Testosterone	57	260	85	**402**	
Doping	3	77	5	**85**	
Anabolic	145	120	9	**274**	
Trigonella foenum-graecum	1,131	2.375	1.757	**5.263**	**27.0**
Testosterone	19	129	27	**175**	
Doping	0	2	0	**2**	
Anabolic	520	78	1	**599**	
Withania somnifera	1,321	2.666	2.010	**5.997**	**30.0**
Testosterone	17	174	19	**210**	
Doping	0	59	0	**59**	
Anabolic	593	138	8	**739**	
Total articles				**19,822**	**100.0**

no impact on the urinary testosterone: epitestosterone ratio (T:E), used in routine doping analysis to detect exogenous testosterone abuse. There were no significant changes in liver and kidney function tests after supplementation.

The roots of *L. meyenii* are popularly used for their aphrodisiac and tonic properties. It has been used as a dietary supplement due to its potential ergogenic and sexual effects by stimulating testosterone production[28]. Chemically, *L. meyenii* produces polysaccharides, polyphenols, imidazole alkaloids (lepidilin A and B), pyrrole alkaloids (macapyrroline A and B), glucosinolates, alkamides, macaenes, macamides (Figure 4)[29]. In a double-blind, randomized, placebo-controlled study of 56 men aged between 21 and 56, administered 1,500 mg or 3,000 mg of maca root for 12 weeks, Gonzales et al.[28] observed that maca had no effect on any of the hormones studied (LH, follicle-stimulating hormone, prolactin, 17-alpha hydroxyprogesterone, and 17-beta estradiol) and that serum



Source: Prepared by the authors based on the references consulted, 2023

Figure 4. Chemical profile of the main anabolic plant drugs dispensed by the magistral pharmacy network.

testosterone levels were not affected by treatment in humans. On the other hand, Ohta et al.[30] showed that guinea pigs fed maca hydroalcoholic extract powder for six weeks increased the weight of the reproductive organs, and increased serum concentrations of testosterone and LH. This increase in testosterone levels may be related to the greater capacity of Leydig cells to produce testosterone.

Despite our data showing that *M. pruriens* was the most commonly used APD to mimic anabolic action, to date there has been no scientific proof in humans of its supplementation for gaining muscle mass and improving physical performance. However, pre-clinical studies in rats showed that administration of the aqueous extract of *M. pruriens* seeds showed testosterone-like activity and an increase in total serum proteins, total cholesterol, and HDL cholesterol, with no adverse effects on serum LDL cholesterol, liver or kidney function[31]. Another study analyzed the androgenic activity of *Mucuna*, observing an increase in the weights of the testes, epididymis, seminal vesicle and prostate of the rats that received the treatment. Serum and testicular testosterone levels, epididymal and testicular protein content and cholesterol increased significantly[32].

All the plant organs of *M. pruriens* have valuable medicinal properties, the main components being the amino acid L-DOPA and isoquinoline alkaloids such as mucunin, mucunadin, mucuadin, and prurienin, as well as other components such as ß-sitosterol, glutathione, lecine, venolic, and gallic acids[33]. The possible mechanism of action of androgenic activity is that *M. pruriens* is able to stimulate the synthesis of androgenic hormones, such as serum and testicular testosterone, but more studies are needed to confirm this hypothesis[34]. Another possible mechanism is that *Mucuna* is a source of L-DOPA (Figure 4), which can further stimulate gonadotropin-releasing hormone (GnRH) after crossing the blood-brain barrier. In the hypothalamic-pituitary-testicular axis, GnRH will further stimulate the production of follicle-stimulating hormone (FSH) and LH in the anterior pituitary gland, which will further stimulate Sertoli cells and Leydig cells, respectively. FSH will increase spermatogenesis and LH testosterone levels[35].

The third most prescribed APD with the most scientific studies was *T. terrestris*. It is a nutritional supplement popular with athletes and physically active people to increase muscle mass gain, strength and performance, as it increases testosterone levels. According to Saudan et al.[36], the steroid saponin protodioscin (Figure 4) is responsible for increasing testosterone, DHEA and LH levels. Studies with *Tribulus* extracts on blood androgens between humans and animals have been contradictory. Ma et al.[37] showed that *T. terrestris* administered to male boxers had no significant influence on serum testosterone concentrations, strength and lean body mass. They observed that the use of 1,250 mg containing *Tribulus* extracts did not alter muscle mass and plasma levels of testosterone, dihydrotestosterone (DHT) and insulin-like growth factor type 1 (IGF-1), but

that there was significant relief of muscle damage and promoted anaerobic performance in trained male boxers, which may be associated with a decrease in IGF I-binding protein type 3 (IGFBP-3) rather than the androgenic property in plasma. A study by Fernàndez et al.[38] revealed that plasma testosterone levels were not affected and there was no improvement in the performance or body composition of male boxers and crossfitters after supplementation with *T. terrestris*.

T. foenum-groecum seed extract was the second APD with the most published scientific articles and the second least prescribed APD. According to data from the magistral pharmacy's storeroom, fenugreek is the most expensive APD compared to the other APDs surveyed, which may explain the lower number of prescriptions. In 2015, Rao et al.[39] showed that fenugreek supplementation in 80 women aged 20 to 49 led to a significant increase in free testosterone and estradiol and had a positive effect on increasing sexual function in healthy menstruating women with low self-reported sexual function. The following year, Wankhede and Mohan[40] conducted a randomized, double-blind, placebo-controlled study in 60 male subjects to evaluate the efficacy and safety of the glycoside fraction of fenugreek seeds on physiological parameters related to muscle anabolism, androgenic hormones and fat during an eight-week resistance training program. An increase in the concentration of free testosterone (98.7%) compared to baseline (17.76 to 35.29 ng/dL, $p < 0.001$) was observed, as well as an increase in muscle strength, a reduction in body fat and muscular endurance.

Fenugreek is certified as an active ingredient, recognized as safe (acronym GRAS) which is a Food and Drug Administration (FDA) designation indicating the safety of the active ingredient. Therefore, the risk of inherent toxicity is very low. Diosgenin (Figure 4) which, according to the Chemical Entities of Biological Interest (ChEBI) database, is a steroid sapogenin, being a spirostane substituted by a hydroxyl group in the 3 beta position, is used as a starting point for the commercial synthesis of various steroids, including cortisone, pregnenolone, and progesterone. It is responsible for anabolic, fat-burning activity and possibly plays an important role in the synthesis of various sex hormones[40]. In addition, other potential mechanisms that may increase serum testosterone include stimulation of pulsatile GnRH/LH, increased testicular sensitivity to LH and increased testosterone synthesis or reduction of testosterone catabolism by inhibiting 5α-reductase (enzyme that converts testosterone).

Consumption of 300 mg of *W. somnifera* root extract in a randomized study led to a significant increase in muscle strength during exercise and in muscle mass[41]. In addition, testosterone levels increased significantly (before intervention: 630.45 ng/dL/after intervention: 726.64 ng/dL). In another randomized study, Lopresti[42] showed that ashwagandha intake was associated with an 18% greater increase in dehydroepiandrosterone sulphate DHEA-S ($p = 0.005$) and a 14.7% increase in testosterone ($p = 0.010$) compared to placebo.

Vitanolides have been isolated from *W. somnifera*, which are secondary metabolites derived from 22 or 23-hydroxyergostan-26-oic acids (steroids) with δ-lactones (22,26) or γ-lactones (23,26), designated as vitanolides A and B, respectively (Figure 4), responsible for their direct action on muscle development, indicated for supplementation in resistance training and improvements in physical performance[43]. It also acts to increase testosterone levels, which leads to muscle growth and decreases cortisol levels which, as a catabolic agent, decreases muscle mass. It has beneficial effects on mitochondrial energy levels and is able to reduce the activity of the Mg^{2+} -dependent ATPase enzyme responsible for breaking down ATP, thus preserving energy levels in our bodies[41]. In addition, it acts on the activity of the hypothalamic-pituitary-adrenal (HPA) axis and on the activity of gonadotrophin-releasing hormone (GnRH) which promotes an increase in DHEA and testosterone concentrations causing the anabolic effect[43]. It also prevents the stress-induced decrease in testosterone levels mediated by cortisol, as well as exerting an inhibitory action on prolactin in sperm production. These mechanisms normalize levels of male reproductive hormones[44].

The Chart shows the main information available in the scientific articles analyzed in the previous paragraphs for the eight APDs analyzed here.

In general, the effect of herbal medicines on testosterone levels and on increasing physical performance needs more clinical studies to assess the effectiveness of the anabolic activity of plant drugs. Increasing testosterone levels through APDs is interesting because it is a natural alternative to hormone replacement therapy and may present greater safety and fewer adverse effects when compared to anabolic steroids. In addition, prescriptions of these APDs are likely to increase due to the recent Federal Council of Medicine Resolution No. 2,333 of April 11, 2023, which prohibits the medical prescription of steroids and anabolic steroids for aesthetic purposes, muscle mass gain and sports performance[45]. The world organizations that control narcotic substances that can adulterate physical performance must be alert to new trends in the use of herbal medicines to obtain anabolic results.

Popular use and traditional use with the manipulation of plant drugs are not enough to validate medicinal plants as effective and safe medicines. In this sense, medicinal plants are no different from any other synthetic drug, and the recommendation or official authorization of their medicinal use must be based on experimental evidence of their efficacy, safety, and possible drug interactions[46].

CONCLUSIONS

The anabolic action of the plant drugs analyzed in this article still needs further clinical studies to determine their efficacy and safety. Among all the prescriptions analyzed, *Mucuna pruriens* was the most prescribed plant drug, although our bibliographic survey data revealed that, of the APDs analyzed, this is one

Chart. Summary of the clinical studies for the plants with possible anabolic activities included in this work.

Medicinal plants	Type of study	Population	Intervention	Results
Ajuga turkestanica	Pre-clinical study	Aged male C57BL/6 mice	50 mg/kg/day of *A. turkestanica*	It did not alter body, muscle or organ mass. Protein synthesis signaling markers remained unchanged[23]
Eurycoma longifolia	Randomized, double-blind, placebo-controlled study	45 men with androgen deficiency (47.38 ± 5.03 years)	G1: control + placebo; G2: Control + *E. longifolia* (200 mg); G3: concurrent training + placebo; G4: concurrent training + *E. longifolia* (200 mg)	43% increase in testosterone levels and reached levels within the normal range for Total Testosterone (> 346 ng/dL)[26]
	Cross-over, double-blind, placebo-controlled study	13 healthy male athletes	400 mg of *E. longifolia* for 6 weeks	It had no impact on the urinary testosterone: epitestosterone ratio[27]
Lepidium meyenii	Double-blind, placebo-controlled, randomized, parallel study	56 men aged between 21 and 56	1,500 mg or 3,000 mg maca root extract	Maca root had no effect on any of the hormones studied (luteinizing hormone, follicle-stimulating hormone, prolactin, 17-alpha hydroxyprogesterone, testosterone and 17-beta oestradiol), nor did the hormones show changes over time[28]
	Pre-clinical studies	Eight male mice	Feeding maca hydroalcoholic extract powder for 6 weeks	Increases serum testosterone concentration[30]
Mucuna pruriens	Pre-clinical study	48 male mice	Groups A and B: oral route è ethanolic and aqueous extracts of *M. pruriens* seeds (500 mg/kg) Group C: systemic route è Testosterone (2.5 mg/kg) Group D: controls	Group A and B mice had higher serum concentrations of testosterone, total serum proteins, total cholesterol and HDL cholesterol when compared to controls. However, there was no difference with guinea pigs in group C[31]
	Pre-clinical studies	Male albino Wistar rats	Two groups Group A: doses of methanolic extract of *M. pruriens* seed (1,000 mg/kg) Group B: *Mucuna* extract (1,500 mg/kg) 30 days	Increased relative testicular weight, serum and testicular testosterone levels, and protein levels in the testis and epididymis. The extracts have androgenic activity[32]
Tribulus terrestris	Placebo-controlled clinical study	15 male boxers	*T. terrestris* capsule 2x/day (1,250 mg) for 6 weeks	It did not alter muscle mass and plasma levels of testosterone, DHT and IGF-1, but significantly alleviated muscle damage and promoted anaerobic performance, which may be associated with a decrease in IGFBP-3 rather than androgenic properties[37]
	Randomized, single-blind, placebo-controlled study	30 healthy men trained in *CrossFit®*	770 mg of *Tribulus* or a placebo daily for 6 weeks	It had no impact on improving performance or body composition in male athletes. However, *T. terrestris* supplementation may act as a testosterone booster, aiding recovery after physical loads and mitigating fatigue[38]
Trigonella foenum-graecum	Randomized, double-blind, placebo-controlled study	60 males	1 fenugreek capsule, 300 mg, twice a day or placebo for 8 weeks	An increase in the concentration of free testosterone (98.7%) compared to baseline (17.76 to 35.29 ng/dL, $p < 0.001$), as well as an increase in muscle strength, a reduction in body fat, muscle endurance and serum creatinine levels.[40]
	Double-blind, randomized, placebo-controlled study	80 women, aged between 20 and 49	Standardized extract of *T. foenum-graecum*, 600 mg/day or placebo for 8 weeks	Significant increase in free testosterone and estradiol, as well as sexual desire and arousal compared to the placebo group[39]
Withania somnifera	Randomized, prospective, double-blind, placebo-controlled clinical study	57 young men (18-50 years old)	300 mg ashwagandha root extract, 2x/day, 8 weeks	Increase in testosterone level (before intervention: 630.45 ng/dL/after intervention: 726.64 ng/dL) Increased muscle strength in the arm (before: 51.96 cm^2/after: 60.85 cm^2) Reduced muscle damage (before: 1,478.88 U/L/after: 16.20 U/L) 3.5% reduction in fat percentage[41]
	Cross-over, randomized, double-blind, placebo-controlled study	57 healthy men (40-70 years old)	Ashwagandha extract providing 21 mg vitanolide per day, 8 weeks	14.7% increase in testosterone levels 18.0% increase in DHEA-S[42]

of the species with the lowest number of published articles. It is worth noting that these plant drugs are not registered by WADA as prohibited substances. For this reason, manipulated herbal medicines are an alternative for increasing physical performance, even though their efficacy and safety have not been proven.

The use of these anabolic plant drugs should be done with caution, as many of them do not yet have robust scientific data and could become a risk factor for intoxication. In addition, it is not yet possible to say that they are capable of increasing testosterone levels and that they can affect an athlete's physical development in competition.

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Authors' Contribution

Costa RLO - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the paper. Santos MIS - Conception, analysis, data interpretation, and writing of the paper. All the authors approved the final version of the paper.

Conflict of Interest

The authors declare that there is no potential conflict of interest with peers and institutions, political or financial, in this study.

Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.