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Review

Phytotherapeutic Alternatives to the Use of Finasteride and Dutasteride as 5-Alpha Reductase Inhibitors in the Treatment of Androgenetic Alopecia: A Review

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Abstract

Introduction: Androgenetic alopecia is the most common form of hair loss worldwide, occurring due to an excessive response to androgens. Its etiology is chronic and influenced by genetic and environmental factors, making it particularly challenging to treat. The primary treatment method currently involves the use of finasteride or dutasteride, which inhibit the 5-alpha-reductase enzyme. This enzyme is responsible for converting testosterone into DHT (dihydrotestosterone), thereby hindering the progression of androgenetic alopecia. Alongside the widespread use of these treatments, concerns have emerged regarding potential side effects associated with this class of drugs. Notably, these include impairments in sexual function and possible psychological disorders, observed in some users. In this context, there has been growing interest in exploring alternative approaches to hair loss treatment using plant-based preparations and/or their active ingredients.

Material and Methods: The method employed for the preparation of this article was an integrative literature review to enable understandings of the use of phytotherapeutic herbs in people with hair loss.

Results and Discussions: Several phytotherapeutic products are known to act against the 5-alpha-reductase enzyme, inhibiting it and reducing hair loss without significant side effects. Plants like Saw palmetto (*Serenoa repens*), Ginseng (*Panax ginseng*), Green tea (*Camellia sinensis*), and Pumpkin seed oil (Cucurbita pepo) are notable for their antiandrogenic effects and have shown beneficial impacts in the treatment of androgenetic alopecia. These could be considered viable options for treating androgenetic alopecia, serving as alternatives to finasteride and dutasteride.

Keywords: Androgenetic alopecia; Phytotherapeutic medications; Side effects; Hair loss.

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1. Introduction

Androgenetic alopecia is a very common chronic dermatological condition, associated with genetic predisposition and characterized by progressive hair loss and thinning. Its incidence is more commonly observed in males after puberty. The mechanism involves the action of dihydrotestosterone (DHT), a sexual hormone derived from the transformation of testosterone by the 5-alpha-reductase enzyme [1]. About 95% of hair loss cases involve androgenic hormones, affecting both men and women. Other reasons include alopecia areata, telogen effluvium, anagen effluvium, and scarring alopecias, some of which are not related to androgens [2].

In men, hair loss typically occurs as a recession of the frontal hairline coupled with thinning at the vertex of the scalp. In women, it presents as hair loss at the vertex of the scalp and

can also occur diffusely [3]. It is believed that androgenetic alopecia is triggered by an abnormal increase in the sensitivity of scalp follicles to circulating androgens [4]. This is due to an increase in the number of androgen receptors, primarily located in the frontal region of the scalp, where hair loss and thinning are more pronounced [5]. It is important to note that, in addition to the physical impact, alopecia causes significant emotional distress and decreases the quality of life, leading to subsequent diseases [6].

The hair growth cycle consists of four distinct phases: anagen or growth; catagen or involution; telogen or rest; and exogen or shedding. About 90% of follicles are in the anagen phase, where they remain for two to seven years. In androgenetic alopecia, there is a shortening of the anagen phase, leading to abnormally short and thin hair. Terminal hairs are replaced by vellus and intermediate hairs, contributing to hair thinning and hair loss. Each follicle has an independent cycle, going through 10 to 30 cycles over a lifetime. On average, each individual has about 100,000 hairs on the scalp, and in healthy people, around 100 to 150 telogen hairs are shed daily. As some hairs are in the anagen phase while others are shedding, the total number of hairs remains stable in the absence of pathology and deficiencies [7].

Diagnosis should be based on history and clinical findings. It is crucial to rule out other etiologies of hair loss, requesting appropriate laboratory tests such as thyroid-stimulating hormone (TSH), complete blood count, ferritin, vitamin D, and gynecological history for women. [8]. The most specific characteristic in patients with androgenetic alopecia is a variation in hair shaft diameter of more than 20%. Concurrently, there is an increase in the proportion of vellus hairs and yellow dots, representing hypertrophy of the sebaceous glands [9].

There are numerous treatment options currently available for people with androgenetic alopecia. Minoxidil is a common treatment choice and has an arteriolar vasodilator effect, inducing cell proliferation. It also increases vascular endothelial growth factor in dermal papilla cells, extending the duration of the anagen phase of the hair cycle [10]. Another commonly used alternative in patients with androgenetic alopecia is the use of 5-alpha reductase inhibitor medications. The best-known are finasteride and dutasteride. Finasteride's mechanism of action is based on the selective competitive inhibition of the type 2 5-alpha-reductase enzyme, preventing the conversion of testosterone to its more potent form, dihydrotestosterone (DHT), thereby reducing serum levels [11]. Although therapy based on oral finasteride is well tolerated, its prolonged use in some patients presents adverse sexual and mental effects, such as erectile dysfunction, loss of libido, and an increase in cases of depression [12].

In this scenario, aiming to reduce the undesirable effects generated by pharmaceuticals, another alternative emerges: phytotherapeutic medications. As they are natural drugs, they have several advantages, such as patient adherence, fewer side effects, and a broader spectrum of activity. However, this type of therapy has a higher therapeutic failure rate and is constantly being modified according to new studies [13]. There are various plants and extracts used in different parts of the world to promote hair growth, and some phytotherapeutic products are acclaimed for their significant activity in this regard. They are also used in polyherbal mixtures for various purposes such as anti-dandruff agents, conditioners, lice infection, and in the treatment of androgenetic alopecia [14].

Within this context, the aim of this work is to conduct a literature review and identify which phytotherapeutics act on the 5-alpha reductase enzyme for the treatment of androgenetic alopecia and how they work.

2. Materials and Methods

The method used for the preparation of this article was an integrative literature review to enable understanding of the use of phytotherapeutic herbs in individuals with hair loss. The work in question was conducted over the months of December and January 2023. For this purpose, articles on the topic were sought in the following medical journals: Google Scholar and the National Library of Medicine (PubMed), using the Health Science Descriptors (DeCS): Alopecia, hair loss, phytotherapeutic medications, Sabal serrulatum, Panax, Cucurbita Pepo, Green Tea, in Portuguese and English.

The inclusion criteria defined were content published between 2012 to 2022, and content focusing on the use of phytotherapeutic herbs in the management of patients with androgenetic alopecia and the evaluation of improvement in their condition. At the end of the search and selection of articles for content analysis, 16 articles were selected that encompassed the topic to be developed. Articles that were not compatible with the desired theme were excluded, as well as those where it was not possible to obtain full-text access.

3. Review and Discussion

There have been several clinical trials evaluating the use of herbs for the treatment of androgenetic alopecia. The most significant evidence for promoting hair growth has been attributed to certain herbs, including *Serenoa repens* (Saw palmetto), *Panax ginseng* (ginseng), *Curcubita pepo* (pumpkin seed), among other species. Generally, the effects of these herbs on hair growth are possibly due to the inhibition of the 5-alpha-reductase enzyme [15].

The aforementioned plants and those most extensively researched with the aim of promoting hair growth will be described below.

3.1 Saw Palmetto

Saw Palmetto, derived from the plant Serenoa repens found mainly in the subtropical region of the United States, is widely used as an alternative treatment for benign prostatic hyperplasia and, more recently, for androgenetic alopecia. The recommended dose is 160 mg twice a day [16]. The primary chemical components found in its extract include fatty acids like lauric acid, myristic acid, and oleic acid, phytosterols, carotenoids, tannins, various sugars, and beta-sitosterol. Fatty acids, constituting about 85% of the extract, are believed to be primarily responsible for its therapeutic effect, along with beta-sitosterol [17].

Saw Palmetto acts as a competitive and non-selective inhibitor of both isoforms of the 5-alpha-reductase enzyme, preventing the nuclear uptake of dihydrotestosterone (DHT) and reducing DHT's binding capacity to androgen receptors by approximately 50%, thereby mitigating the actions of this hormone [16]. Another mechanism of action involves the activation of estrogen receptors, which stimulate the mitosis of the matrix through the activation of the adenylate cyclase pathway. This favors the normalization of the catagen phase and the maintenance of the anagen phase of the hair cycle [17]. Additionally, Saw Palmetto increases the activity of the enzyme 3-beta-hydroxysteroid dehydrogenase, which converts DHT into a weaker metabolite, androstanediol [16].

A randomized clinical trial conducted on 100 patients with androgenetic alopecia divided participants into two groups: one treated with 320 mg of Saw Palmetto and the other with 1 mg of finasteride for 24 months. The results showed that about 40% of the Saw Palmetto group experienced significant hair growth, compared to 68% in the finasteride group. It was also observed that finasteride acts on both the frontal region and the vertex of the scalp, while Saw Palmetto primarily affects the vertex, making it suitable for mild to moderate cases of androgenetic alopecia [17]. The antiandrogenic properties, minimal side effect profile, and low risk of drug interactions compared to synthetic 5-alpha reductase inhibitors make Saw Palmetto a valid option for complementary treatment of alopecia, either as monotherapy or in combination with other supplements in topical and oral formulations [18].

3.2 Ginseng

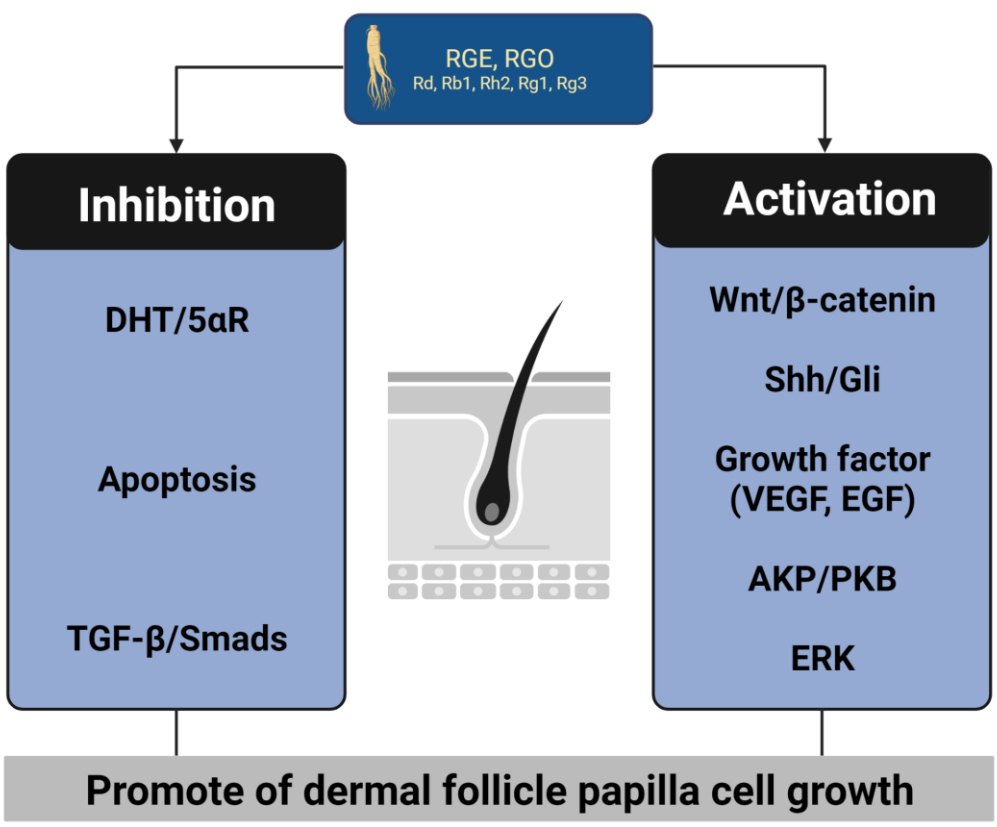
Ginseng (*Panax ginseng*) comprises a genus of 11 species of roots generally found in the milder climates of Asia and Russia. There are two types of ginseng roots: red and white, each processed in different ways. Red ginseng is believed to have a greater variety and quantity of active ingredients, thus exhibiting more significant physiological activity [19]. The range of bioactive constituents found in ginseng is vast, among which a group of saponin compounds known as ginsenosides stands out. These are responsible for many of its biological activities, including the potential for hair growth. Ginsenosides are classified into two major groups: protopanaxadiol and protopanaxatriol, each with various subtypes that can be used individually, depending on the therapeutic objective [20].

Topical application of ginseng extract or isolated ginsenosides can enhance hair growth in several ways, notably through the inhibition of the 5-alpha-reductase enzyme. Red ginseng contains considerable amounts of the ginsenosides Ro, Rg3, and Rd, which are the main active principles responsible for enzyme inhibition and hair growth [21]. Another observed mechanism is the potential increase in the proliferation of human dermal papilla cells, activating two pathways: the extracellular signal-regulated kinase pathway and the AKT signaling pathway, inhibiting the transcription of the androgen receptor induced by DHT. There is also a reported potential effect on the proliferation and modulation of apoptosis of hair follicle cells, as well as on the inflammatory activity at the hair root [22].

Ryu [23] reported that combined treatment with topical Minoxidil and oral red ginseng is more effective than using Minoxidil alone to promote hair growth. Therefore, the use of ginseng or its specific ginsenosides can be recommended as a way to complement established treatment methods [23]. Figure 1 demonstrates the potential molecular targets of ginseng in

hair growth and loss. Ginseng exhibits therapeutic properties for hair growth and hair loss prevention through the inhibition of apoptosis in hair follicle cells.

Figure 1. Potential molecular targets of ginseng.



3. Green tea

Green tea is derived from the leaves of the *Camellia sinensis* plant, commonly found in Asian and Middle Eastern countries. Its constituents are largely composed of potent antioxidants such as polyphenols and flavonoids, which include catechins and their derivatives like epicatechin, epigallocatechin gallate, epigallocatechins, and epicatechin gallate [24]. The catechin known as epigallocatechin gallate has various effects related to hair growth. These include antiandrogenic effects due to the inhibition of the activity of type 1 5-alpha-reductase enzyme, prolongation of the anagen phase, and inhibition of apoptosis in dermal papillae, actions that prevent hair loss [19].

Epigallocatechin, found in high quantities in green tea, has the potential to prevent the depression of IGF-1 levels at the follicle level. IGF-1 prevents hair follicles from transitioning from the anagen to catagen phase and stimulates the transition from the telogen to anagen phase in the hair cycle [25]. The effects of polyphenols found in green tea were examined in an experimental study involving 60 black mice with spontaneous hair loss on their heads, necks, and other areas. One group received drinking water with green tea polyphenol extract for six months and showed significant hair growth in 33% of the mice. No growth was observed in the second group that only received regular water. More studies on green tea, particularly clinical trials in humans, are necessary [19].

It's important to note that the benefits of green tea extend far beyond its role in hair loss, as it is used for various purposes. Among these, its intense antioxidant effect, antimicrobial and antiviral activity, neuroprotective and cardioprotective functions, and its significant role in combating obesity stand out. This broad spectrum of action and the evidence presented for the treatment of androgenetic alopecia support the applicability of green tea in various medical areas [18].

3. Pumpkin seed

Pumpkin, or Cucurbita pepo, the most common species, is a plant in the Cucurbitaceae family used for various medical purposes. Pumpkin seed oil, derived from the seeds, is rich in unsaturated fatty acids, beta-carotene, lutein, gamma and beta-tocopherols, squalene, and phytosterols [26]. Among its biological effects, the most notable are its strong hypotriglyceridemic, antidiabetic, antibacterial, antioxidant, and antiandrogenic properties. The latter is attributed to the phytosterols present in large quantities in pumpkin seed oil. It has been reported that these phytosterols act by inhibiting the 5-alpha-reductase enzyme, thereby reducing serum DHT levels, with greater intensity at a dose of 400 mg per day [27].

A randomized, double-blind, placebo-controlled clinical trial examined the efficacy and potential side effects of pumpkin seed oil in male patients with mild to moderate androgenetic alopecia. One group received 400 mg of pumpkin seed oil daily for 24 weeks, while the control group received a placebo. The evaluation was conducted using scalp hair count. An average increase of 40% in hair count was observed in the experimental group, compared to a 10% increase in the placebo group. No adverse effects were reported in this study [27]. Pumpkin seed oil had a positive anabolic effect on hair growth, possibly through the mechanism of inhibiting the 5-alpha-reductase enzyme. However, it is important to note that DHT levels were not measured to confirm this action of pumpkin seed oil, necessitating further studies to clarify its mechanism [27].

Beyond the previously mentioned phytotherapeutic herbs, there are other species capable of inhibiting the 5-alpha-reductase enzyme. Curcuma aeruginosa, a plant native to South Asia, contains sesquiterpenes, which potentially inhibit the conversion of testosterone to DHT [28]. Another alternative is Licorice (*Glycyrrhiza glabra*), widely cultivated in India. The extract has been identified with compounds that function to antagonize testosterone, including glycosides, terpenoids, phenolics, and flavonoids. Additionally, phytosterols, found in large quantities in licorice, may inhibit certain enzymes, including 5-alpha-reductase [29].

Finally, *Pygeum africanum*, an extract from the bark of the African plum tree, has been used in Europe since 1969 for the treatment of benign prostatic hyperplasia and more recently for androgenetic alopecia. Its constituents include phytosterols and beta-sitosterol, both possessing inhibitory properties on the 5-alpha-reductase enzyme [30]. An important consideration in the use of phytotherapeutics, whether for androgenetic alopecia or other purposes, is their quality. Phytotherapeutic products are those derived from medicinal plants and can be used in forms such as tinctures, fluid extracts, dry extracts, among other extractive forms.

The first point to note is that, as they are natural products, there will be variations due to different conditions like soil, climate, irrigation, altitude, among others. For this reason, it is very important to opt for standardized phytotherapeutic preparations, i.e., preparations that maintain consistency in the dosage of active ingredients, with qualitative and quantitative characterization of their active principles, providing quality, effectiveness, and safety requirements. Regarding side effects, Ferreira et al. [31] report a lower incidence related to the use of phytotherapeutics. However, they are not free of toxicity. Few studies compare and evaluate the potential for adverse effects of phytotherapeutics compared to conventional therapy. However, when examining scientific articles that describe these effects separately, those discussing the medications dutasteride and finasteride have significantly higher reports of adverse effects compared to phytotherapeutics.

Another important point is the patient's perception of the treatment. There is a large portion of the population that prefers natural products and often refuses to use medications like the ones mentioned, due to their associated reputation.

3. Conclussion

Based on the information presented, it is possible to conclude that there are viable phytotherapeutic products for the treatment of androgenetic alopecia, serving as alternatives to medications like finasteride and dutasteride. The most frequently mentioned phytotherapeutics in the literature for this purpose are Saw palmetto (*Serenoa repens*), Ginseng (*Panax ginseng*), Green tea (*Camellia sinensis*), and Pumpkin seed oil (*Cucurbita pepo*). It is important to emphasize that the quality and method of use of phytotherapeutics are directly related to their efficacy and safety and should be considered with great rigor.

Further studies, particularly in humans, are necessary to supplement information on the mechanism of action, duration of use, effectiveness, and safety not only of the phytotherapeutics mentioned in this study but also of other species used for this purpose.

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