

REVIEW

Advances in the treatment of male androgenetic alopecia: current options and emerging therapies

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ABSTRACT

INTRODUCTION: Androgenetic alopecia (AGA), or pattern hair loss, is the most common form of hair loss worldwide. It is primarily caused by genetic and hormonal factors, particularly the action of dihydrotestosterone (DHT) on hair follicles.

EVIDENCE ACQUISITION: A comprehensive literature search on PubMed and Google Scholar was conducted until October 31, 2024, using keywords related to male AGA and its treatments. Relevant reviews, meta-analyses, clinical trials, and case studies in English were selected and analyzed to enhance the quality of the research. This review is based solely on existing studies and does not include new human or animal research conducted by the authors.

EVIDENCE SYNTHESIS: This review thoroughly examined and analyzed 149 articles to provide a detailed presentation of the evidence.

CONCLUSIONS: This article examines both established and emerging therapies for AGA. We recommend initiating treatment with topical minoxidil and oral finasteride, as these are extensively researched and FDA-approved options for male AGA. For patients who do not respond well or cannot tolerate these treatments, clinicians may explore alternative therapies and approaches.

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KEY WORDS: Androgenetic alopecia; Alopecia; Male Androgenetic Alopecia.

Introduction

Androgenetic alopecia (AGA), commonly referred to as pattern hair loss, is the most prevalent form of hair loss affecting both men and women globally.^{1,2} Characterized by a progressive thinning of hair, AGA manifests differently between sexes: men typically experience a receding hairline and thinning at the crown, while women often exhibit diffuse thinning across the scalp.^{3,4} This condition is primarily driven by genetic predisposition and hormonal influences, particularly the action of dihydrotestosterone (DHT) on hair follicles, leading to their miniaturization and eventual loss.³

This article provides a comprehensive review of the pathogenesis of AGA and explores advancements in the treatment of male AGA, highlighting current approaches and emerging therapies.

Evidence acquisition

A literature search was conducted on PubMed and Google Scholar up to October 31st, 2024, using the following key words: “male AGA,” “female pattern hair loss,” “AGA emerging therapies,” “AGA pathogenesis,” “oral finasteride,” “oral dutasteride,” “oral minoxidil,” “topical minoxidil,” “topical finasteride,” “topical dutasteride,” “cetirizine,” “low-level laser therapy,” “platelet-rich plasma,” “microneedling,” “mesotherapy,” “stem cell/exosome,” “hair transplantation,” and “natural products for AGA.” In our review, we examined reviews, meta-analyses, clinical trials, real-life studies, and case reports and series, selecting the most pertinent articles. We only included manuscripts written in English. The texts and abstracts of the chosen articles were revised to improve the research quality. This review

article relies on previously completed studies and does not involve any human or animal trials conducted by the authors.

Evidence synthesis

This review examined and analyzed a total of 149 articles to present the evidence in detail.

Pathogenesis of androgenetic alopecia (AGA)

AGA, commonly known as male-pattern baldness or female-pattern hair loss, is a prevalent form of hair loss that affects both men and women. Its pathogenesis is multifactorial, involving genetic, hormonal, and cellular factors that collectively lead to hair follicle miniaturization and progressive hair thinning.^{5, 6} Understanding these mechanisms is important for developing targeted therapies and treatments.

Genetic factors

Genetic predisposition plays a pivotal role in AGA. The condition follows a polygenic inheritance pattern, meaning that multiple genes contribute to its development. The androgen receptor (AR) gene, located on the X chromosome, is particularly significant.^{6, 7} Variations in the AR gene influence the sensitivity of hair follicles to androgens, particularly dihydrotestosterone (DHT).⁷ High levels of DHT or an increased sensitivity to this hormone can precipitate hair loss.^{5, 7}

Recent studies have also identified other genetic loci associated with AGA, such as those linked to the Wnt signaling pathway and follicular growth regulation.⁶ However, the complexity of genetic interactions in AGA means that understanding the precise role of each gene remains an ongoing area of research.⁵⁻⁷

Hormonal influence

The role of androgens, particularly testosterone and its more potent derivative DHT, is central to AGA. In genetically susceptible individuals, DHT binds to androgen receptors in hair follicles, triggering a cascade of events that lead to follicular miniaturization.⁵ DHT is produced through the action of 5-alpha reductase, an enzyme that converts testosterone into its more potent form. Elevated levels of DHT or increased 5-alpha reductase activity can exacerbate hair loss by shortening the anagen (growth) phase of the hair cycle and prolonging the telogen (resting) phase.^{5, 7}

Cellular mechanisms

At the cellular level, AGA is characterized by the progressive miniaturization of hair follicles. This process involves several key mechanisms such as follicular miniaturization, inflammatory processes, and altered hair cycle dynamics.

In AGA, susceptible hair follicles undergo a process of miniaturization, where the diameter of the hair shaft decreases, and the follicle size diminishes.^{5, 7} This results in shorter, finer hairs known as vellus hairs. Miniaturization is thought to be driven by the impact of androgens on the follicular matrix cells and dermal papilla, which are critical for follicle growth and regeneration.^{5, 7, 8}

There is evidence suggesting that inflammatory processes may contribute to follicular damage and hair loss. The presence of inflammatory cytokines and changes in the immune microenvironment of the scalp can exacerbate follicular damage and contribute to the progression of AGA.⁹

Altered hair cycle dynamics

In AGA, the hair growth cycle is disrupted.⁸ The anagen phase, which is responsible for hair growth, is shortened, while the telogen phase is prolonged.^{5, 7} This alteration in the hair cycle dynamics results in decreased hair density and increased shedding.

Oral therapies

Oral finasteride

HISTORY AND APPROVAL STATUS

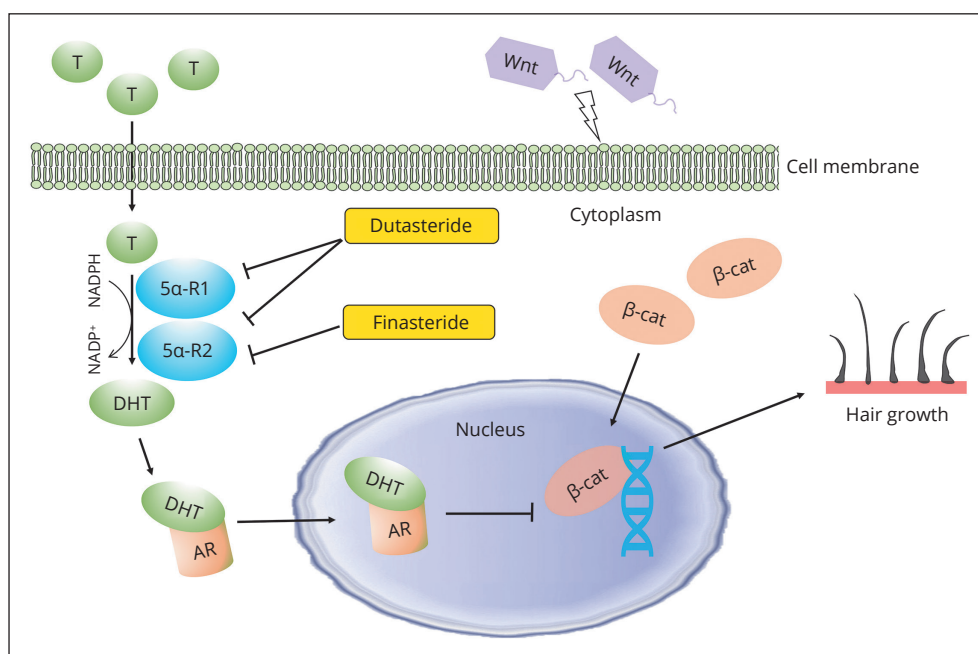
Finasteride was initially developed to treat benign prostatic hyperplasia (BPH) and received FDA approval in 1992 under the brand name Proscar.⁴ In 1997, the FDA expanded its approval to include the treatment of male AGA at a lower dosage of 1 mg/day, marketed as Propecia. This decision was based on clinical trials demonstrating that finasteride effectively reduced hair loss and promoted regrowth in men with AGA.² Currently, finasteride is FDA-approved only for use in men with AGA.² However, some clinicians use finasteride off-label to treat female pattern hair loss in post-menopausal women.^{2, 3}

MECHANISM OF ACTION

Finasteride acts as a 5-alpha reductase inhibitor, which inhibits the enzyme that converts testosterone into dihydrotestosterone (DHT), a hormone linked with hair loss and enlargement of prostate (Figure 1).³ It specifically targets the type II isoform of 5-alpha reductase, which is primarily found in scalp hair follicles.⁴ This inhibition significantly

Figure 1.—Finasteride blocks the conversion of testosterone to DHT by inhibiting 5 α -reductase type II, while dutasteride inhibits both type I and type II. Both drugs may prevent hair loss, potentially through the Wnt/ β -catenin signaling pathway (modified from Gupta and Talukder).¹⁰

T: testosterone; 5 α -R1: 5 α -reductase type I; 5 α -R2: 5 α -reductase type II; DHT: dihydrotestosterone; AR: androgen receptor; β -cat: beta-catenin.



reduces DHT levels in both the serum and scalp.² By lowering DHT concentrations, finasteride promotes hair growth, potentially through the Wnt/ β -catenin signaling pathway.^{2,3}

EFFICACY

Multiple clinical studies have demonstrated the effectiveness of oral finasteride (1 mg/day) in treating male AGA.¹¹⁻¹⁵ In a randomized, placebo-controlled, double-blind trial, 93 men received finasteride 1 mg/day for 48 weeks, while the control group (N=91) was given a placebo for the same duration.¹² After 48 weeks, the finasteride group showed an increase in total hair density from 200.0 $\pm$ 5.2 hairs/cm² to 207.4 $\pm$ 5.4 hairs/cm². In contrast, the placebo group experienced a slight decline in hair density, from 195.5 $\pm$ 5.4 hairs/cm² to 186.2 $\pm$ 5.0 hairs/cm².¹² Additionally, Kaufman *et al.* conducted a double-blind, randomized, placebo-controlled clinical trial, which demonstrated that a daily dose of 1 mg finasteride effectively reduced hair loss and promoted hair growth.¹³ Additionally, Kaufman *et al.* conducted a double-blind, randomized, placebo-controlled clinical trial, which showed that a daily dose of 1 mg finasteride effectively reduced hair loss and enhanced hair growth. After 12 months of treatment, the difference in total hair density between the finasteride group and the placebo group was 21.12 $\pm$ 0.87 hairs/cm².¹³

A placebo-controlled, double-blind clinical trial reported a total hair density difference of 11.6 $\pm$ 2.0 hairs/cm²

in the frontal scalp between the finasteride 1 mg/day and placebo groups after 12 months of treatment ($P<0.001$), with the finasteride group showing a significant increase in frontal scalp hair count.¹⁴ Additionally, a dose-ranging, placebo-controlled, double-blind trial demonstrated that finasteride 1 mg/day for 12 months was more effective than doses of 0.2 mg/day and 0.01 mg/day.¹⁵

SAFETY

Although finasteride is typically safe, side effects include decreased libido, erectile dysfunction, ejaculation disorders and mood disorders. Most side effects are mild and may lessen over time.^{3,4} However, a small percentage of men might experience long-standing sexual dysfunction and neuropsychiatric symptoms even after stopping the medication.² This condition, known as post-finasteride syndrome (PFS), is still being researched.² Finasteride is contraindicated for pregnant women and women of child-bearing potential due to the risk of birth defects.⁴ However, some clinicians use finasteride off-label for treating FPHL in postmenopausal women.⁴

Oral dutasteride

HISTORY AND APPROVAL STATUS

Dutasteride is not yet FDA-approved for treating male AGA, though clinicians often use it off-label for this pur-

pose. However, Japan and South Korea approved it for treating male AGA in 2015 and 2019, respectively.^{2, 3} Dutasteride, developed by GlaxoSmithKline and patented in 1993, was designed as a more effective alternative to finasteride for treating BPH. The FDA approved dutasteride for BPH treatment in men in 2001.^{2, 3}

MECHANISM OF ACTION

Similar to finasteride, dutasteride is a 5-alpha reductase inhibitor.¹⁶ However, dutasteride uniquely inhibits both type I and type II isoforms of 5-alpha reductase, whereas finasteride only inhibits the type II isoform (Figure 1).⁴ Dutasteride is more effective at reducing serum and scalp DHT levels compared to finasteride, thereby enhancing hair growth.²

EFFICACY

A randomized, open-label, assessor-blinded study by Shanshanwal and Dhurat found that dutasteride was more effective than finasteride in treating male AGA, with a comparable safety profile.¹⁷ In the study, one group of patients received 0.5 mg of dutasteride daily for 24 weeks, while the other group was given 1 mg of finasteride daily for the same duration.¹⁷ In the dutasteride group, total hair density increased by 23.1 ± 8.4 hairs/cm², and terminal hair density rose by 30.5 ± 12.9 hairs/cm² from baseline after 24 weeks.¹⁷ In the finasteride group, total hair density increased by 4.3 ± 12.5 hairs/cm², and terminal hair density grew by 5.6 ± 13.0 hairs/cm² over the same period.¹⁷

In a Phase III, randomized, double-blind clinical trial, men with AGA were administered either 0.5 mg of dutasteride per day or a placebo for a duration of six months.¹⁸ Dutasteride showed substantially higher efficacy than the placebo.¹⁸ The group treated with dutasteride experienced an increase in total hair density of 12.2 ± 23.6 hairs/cm² from baseline, whereas the placebo group saw an increase of 4.7 ± 16.8 hairs/cm².¹⁸ Sexual dysfunction occurred in 4.1% of those on dutasteride, compared to 2.7% in the placebo group.¹⁸

In another placebo-controlled, randomized, double-blind, dose-ranging study, administering 0.5 mg of dutasteride daily for 24 weeks was found to be more effective than 1 mg of finasteride daily in treating AGA.¹⁹ The side effect profiles of both medications were comparable. In the dutasteride (0.5 mg/day) group, the average increase in total hair count from baseline was 17.2 ± 1.6 hairs/cm², with a mean hair diameter increase of 5.8 ± 0.5 μ m at 24 weeks.¹⁹ In the finasteride group, the average increase in total hair count was 11.2 ± 1.6 hairs/cm², and the mean increase in

hair diameter was 4.0 ± 0.5 μ m.¹⁹ The efficacy of dutasteride was dose dependent.

SAFETY

The side effects associated with dutasteride are similar to those of finasteride and may include impotence, decreased libido, ejaculation disorders, and breast disorders.²⁰ Dutasteride falls under FDA Pregnancy Category X, meaning it should not be used during pregnancy because it can potentially harm the fetus.²¹ Pregnant women should avoid any direct exposure to dutasteride, including handling soft capsules that are broken or damaged.²⁰ Dutasteride can be absorbed through the skin and may result in birth defects in male fetuses, such as genital abnormalities like hypospadias, especially within the first 16 weeks of pregnancy.^{2, 3, 20} Patients with allergies to soy or peanuts should not use dutasteride, as its capsule shells contain soy-derived lecithin.²² Dutasteride can remain in the bloodstream for up to six months after discontinuation. Consequently, men who have taken this medication should wait at least six months after their final dose before donating blood.²³

Oral minoxidil

HISTORY AND APPROVAL STATUS

Research indicates that low-dose oral minoxidil (LDM) can be effective for various forms of alopecia, including male AGA and FPHL.^{1, 24} However, it is currently used off-label and lacks FDA approval.^{1, 24} Minoxidil was originally developed in the 1960s as an antihypertensive medication.^{1, 24} Its hair growth-promoting effects were discovered serendipitously when patients treated for high blood pressure began reporting increased hair growth as a side effect.^{1, 24}

MECHANISM OF ACTION

The exact mechanism by which minoxidil enhances hair growth remains unclear.¹ It is thought to act as a vasodilator, relaxing blood vessels and reducing systolic and diastolic blood pressure, thereby increasing the supply of oxygen and nutrient-rich blood to hair follicles (Figure 2).¹ Minoxidil may also aid hair growth by reducing perifollicular microinflammation. Some studies suggest it stimulates the Wnt/ β -catenin signaling pathway, which is associated with hair growth.¹ Additionally, minoxidil may exhibit anti-androgenic effects and enhance hair growth by prolonging the anagen phase or shortening the telogen phase of the hair cycle.¹

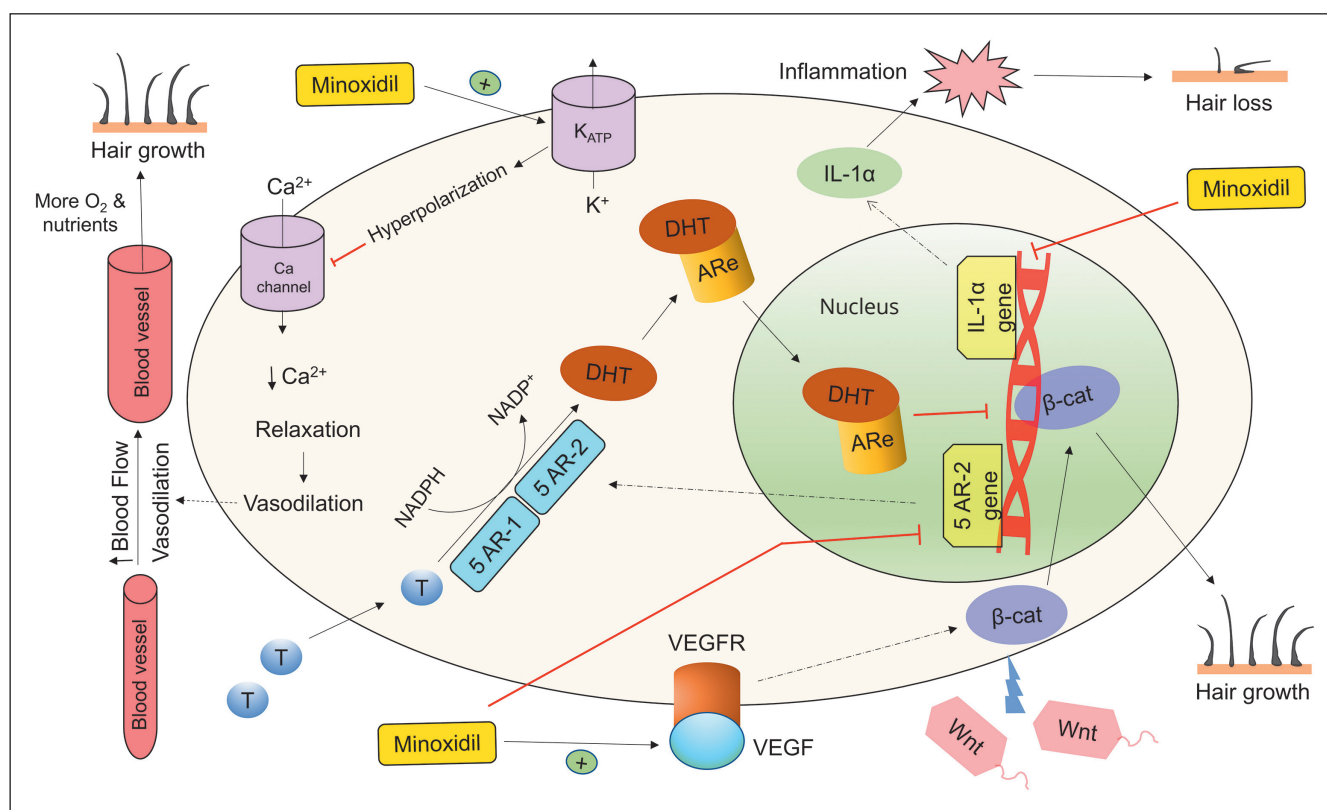


Figure 2.—Proposed mechanism of action of minoxidil. A) Minoxidil stimulates the ATP-sensitive potassium channel, eventually leading to vasodilation. Dilated blood vessels can carry more oxygen and nutrients to the hair follicles, and thus promoting hair growth. B) Minoxidil may down-regulate the expression of the interleukin-1 alpha gene, and thus may reduce perifollicular microinflammation by inhibiting inflammatory mediators such as interleukin-1 alpha, which facilitates hair growth. C) Minoxidil may inhibit the expression of 5 alpha-reductase type II gene, and thus may act as anti-androgen and promote hair growth. D) Minoxidil may also induce wnt/b-catenin signaling pathway by stimulating the release of VEGF in the dermal papilla cell, leading to potentiate hair follicle regeneration (from Gupta *et al.*).²⁴

5 AR-1: 5 alpha-reductase type I; 5 AR-2: 5 alpha-reductase type II; AR: androgen receptor; β -cat: Beta-catenin; Ca: calcium; DHT: dihydrotestosterone; IL-1 α : interleukin-1 alpha; IL-1 α gene: Interleukin-1 alpha gene; K: potassium; NADP⁺: nicotinamide adenine dinucleotide phosphate; NADPH: reduced form of NADP⁺; O₂: oxygen; T: testosterone; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; Wnt: wingless-related integration site.

EFFICACY

Multiple clinical trials have examined minoxidil doses between 0.25 mg and 5 mg. A retrospective study involving 25 male AGA patients who took 0.25 mg/day of minoxidil for 24 weeks showed no significant improvement in total or terminal hair counts.²⁵ The authors suggested that a higher dose of minoxidil might be required to achieve noticeable results. Commonly reported side effects in the study included increased beard density, hypertrichosis, hair shedding, and pedal edema. However, patients did not exhibit changes in mean arterial pressure or experience fainting or dizziness.²⁵

A prospective, open-label, single-arm study evaluated 30 male AGA patients who received 5 mg of minoxidil daily. The findings demonstrated a significant increase in

total hair count after 12 and 24 weeks of treatment.²⁵ Hair growth improvement was more noticeable in the vertex region than in the frontal area. The most common side effect was hypertrichosis, with other side effects including abnormal EKG results, pedal edema, premature ventricular contractions, fatigue, tachycardia, urticaria, and itchy rash.

SAFETY

Side effects of low-dose oral minoxidil (LDOM) can be classified into two categories: predictable, dose-dependent effects (type A) and unpredictable, idiosyncratic reactions (type B). When used to treat alopecia, the most common side effects are hypertrichosis and cardiovascular symptoms. Cardiovascular symptoms encompass side effects such as hypotension, edema, premature ventricular contractions,

fatigue, tachycardia, and ECG abnormalities.²⁵⁻³¹ Rarely, patients have exhibited type B idiosyncratic reactions, including pericardial effusion and generalized anasarca. Notably, ongoing research is exploring whether pericardial effusion truly qualifies as an idiosyncratic reaction.³²⁻³⁶

Topical therapies

Topical minoxidil

HISTORY AND APPROVAL STATUS

The FDA approved the 2% topical minoxidil solution for treating male AGA in 1988, followed by its approval for FPHL in 1992.² In 1996, the FDA authorized over-the-counter (OTC) use of the 2% topical solution for both male AGA and FPHL.² In 1997, the 5% topical minoxidil solution was approved for OTC use in male AGA. The FDA later approved OTC use of 5% minoxidil foam for male AGA in 2006 and for female AGA in 2014.²

EFFICACY

A five-year study evaluating 2% and 3% topical minoxidil in males demonstrated peak hair regrowth at the one-year mark, followed by a gradual decline in subsequent years.³⁷ Despite this decline, the minoxidil solution consistently preserved non-vellus hair regrowth throughout the study period.³⁷ A network meta-analysis ranked the effectiveness of minoxidil treatments for male AGA as follows: oral minoxidil 5 mg/day (SUCRA: 100%), 2% topical solution (SUCRA: 71.34%), 5% topical solution (SUCRA: 67.47%), 5% topical foam (SUCRA: 52.3%), 1% topical foam (SUCRA: 39.84%), and oral minoxidil 0.25 mg/day (SUCRA: 3.06%).²

SAFETY

The side effects of topical minoxidil include scalp pruritus and hypertrichosis.^{1,2} Early hair shedding may occur within the first few weeks of using topical minoxidil, which paradoxically indicates the treatment is working.^{1,2} However, if shedding persists beyond two weeks, it is advisable to consult a physician.^{1,2} This shedding is thought to result from a rapid transition of hair follicles from the telogen (resting) phase to the anagen (growth) phase.^{1,2}

Topical finasteride

HISTORY AND APPROVAL STATUS

Topical finasteride has not yet been approved by the FDA for treating AGA. However, a spray formulation of topical finasteride has received approval in several countries,

including Italy, Germany, Luxembourg, Portugal, and South Korea.^{38, 39} The Spanish pharmaceutical company Almirall has partnered with Difa Cooper in Italy to market this spray under the brand name 'Caretopic' in southern Western Europe. Additionally, Almirall has teamed up with Hikma Pharmaceuticals to distribute it in the Middle East and North Africa, and with Boryung Pharmaceutical to market it in South Korea.

EFFICACY

A phase III randomized clinical trial investigated the efficacy of finasteride topical spray in male patients aged 18 to 40 years with mild to moderate vertex male pattern hair loss.¹¹ A total of 458 patients, of which 323 completed the study, were randomized at 2: 2: 1 into three treatment groups: topical finasteride group (topical finasteride and oral placebo), oral finasteride group (topical placebo and oral finasteride), and placebo group (topical placebo and oral placebo).¹¹ Topical and oral finasteride treatments were 0.25% w/w topical spray (2.275 mg/mL) and a 1 mg oral tablet, respectively.¹¹ Participants in each treatment group were instructed to apply 1-4 sprays (50-200 µL) of the topical solution based on the severity of their hair loss and to take one tablet daily for 24 weeks.¹¹ After 24 weeks, the topical finasteride group showed a significant improvement in target area hair count (TAHC) compared to the placebo group (20.2 vs. 6.7 hairs/cm²; P<0.001). The TAHC improvements were similar between the topical and oral finasteride groups (mean change, 20.2 vs. 21.1 hairs/cm²). However, topical finasteride did not show a significant difference in hair diameter.¹¹

SAFETY

Topical finasteride formulations are generally associated with mild to moderate localized side effects.⁴⁰ Clinical studies have reported side effects such as scalp pruritus, burning, irritation, contact dermatitis, and erythema.⁴¹⁻⁴⁵ Additionally, some users may experience a mild, dry, flaky scalp or a sensation of heaviness at the application site.^{40, 45} A recent phase III clinical trial identified treatment-emergent adverse events (TEAEs) for the placebo, oral, and topical finasteride groups, which included loss or reduction in libido, itching (pruritus), and redness (erythema).¹¹ The incidence of treatment-related TEAEs was 9.9% in the topical finasteride group, 6.6% in the placebo group, and 11.9% in the oral finasteride group.¹¹ Discontinuation rates due to treatment-related TEAEs were 2.8% for the topical finasteride group, 2.2% for the placebo group, and 7.1% for the oral finasteride group.¹¹

Topical dutasteride

HISTORY AND APPROVAL STATUS

Topical dutasteride is not approved yet for treating male AGA.

EFFICACY

A randomized, placebo-controlled trial evaluated the effectiveness of microneedling paired with a 0.01% topical dutasteride solution *versus* microneedling with a saline solution.⁴⁶ The study included 34 male patients with AGA over 20 weeks.⁴⁶ Results showed significant hair growth improvements, including increased hair thickness and density, in 52.9% of patients receiving the dutasteride combination compared to 17.6% in the saline group.⁴⁶ Adverse effects, such as erythema and scalp sensitivity lasting no more than 36 hours, were reported in 88.2% of the saline group and 84.2% of the dutasteride group.⁴⁶

INTRALESIONAL DUTASTERIDE

The use of intralesional dutasteride is less studied. A systematic review compared the intralesional and oral routes of dutasteride administration.⁴⁷⁻⁵⁰ It found that taking 0.5 mg of oral dutasteride daily led to an average increase of 15.9 hairs per cm², whereas intralesional dutasteride resulted in an increase of 7.9 hairs per cm².⁴⁷ This suggests that although both methods are effective, oral administration may be more beneficial for hair growth.⁴⁷

Cetirizine

HISTORY AND APPROVAL STATUS

Cetirizine is a second-generation antihistamine, commonly used to alleviate allergy symptoms, such as sneezing, itching, and runny nose.⁵¹ It was first approved by the FDA under the brand name Zyrtec.⁵² Cetirizine works by blocking histamine H1 receptors, thus reducing allergic reactions.^{51,53} Traditionally, it has not been associated with the treatment of AGA.^{51,53} However, recent studies have explored cetirizine's off-label potential in addressing hair loss.

MECHANISM OF ACTION

The primary mechanism of action of cetirizine is the selective inhibition of peripheral histamine H1 receptors. Histamine plays a role in allergic reactions and inflammation, and cetirizine's blockade of these receptors reduces these symptoms.^{51,53} The proposed mechanism by which cetirizine might affect hair growth involves its potential anti-inflam-

matory and anti-androgenic properties. Although cetirizine is not a conventional treatment for AGA, its ability to reduce inflammation and possibly influence androgen pathways has led researchers to investigate its effects on the health of the hair follicle.⁵³ The hypothesis suggests that by mitigating inflammation and modulating androgen-related pathways, cetirizine could indirectly benefit individuals with AGA.^{51,53-55}

EFFICACY

The efficacy of cetirizine as a treatment for AGA is still under investigation. Current clinical research is limited, and findings are preliminary.⁵⁶ Some studies suggest that cetirizine might have a positive impact on hair growth due to its anti-inflammatory properties, which can improve scalp health and reduce hair follicle inflammation.^{51,54} However, the evidence is not robust enough to establish cetirizine as a first-line treatment for AGA. Most of the current research involves small sample sizes or indirect evidence, and further large-scale, controlled trials are needed to validate its effectiveness. At present, cetirizine is not widely recognized or recommended as a standard treatment for AGA by dermatological or medical guidelines.

SAFETY

Cetirizine is generally considered safe for use in its approved indications as an antihistamine. Common side effects include drowsiness, dry mouth, and headache.^{51,53,54} Its safety profile is well-documented in the context of allergy treatment, and it is generally well-tolerated by patients.⁵² However, when used off-label for AGA, the long-term safety and potential side effects specifically related to hair treatment have not been thoroughly studied. As with any off-label use, the safety of cetirizine for treating AGA should be carefully monitored, and patients should be advised to consult with a healthcare provider before using cetirizine for this purpose.

Other non-systemic therapies

Low-level laser therapy

HISTORY AND APPROVAL STATUS

Exploratory animal studies in the late 1960's provided the first indication that low-level laser therapy (LLLT) had the potential to increase hair growth.^{57,58} While testing the carcinogenicity of a low-power 694 nm ruby laser on mice, Endre Mester, a Hungarian physician, did not observe an induction of cancer in treated mice, but instead, noticed increased hair growth in the shaved target regions.⁵⁷ This

study is among the first recorded “photobiomodulation” effects of LLLT; stimulation of cellular- and tissue-level processing and remodeling.^{57, 58}

Since these exciting preliminary observations, researchers at the National Aeronautics and Space Administration (NASA) looking for a solution to plant growth experiments aboard the International Space Station (ISS) developed the light-emitting diode (LED).⁵⁹ Further exploratory research found that LLLT and LED treatment might reduce inflammation and accelerate wound healing.⁵⁹

Perhaps in part due to public demand for alternatives to traditional drug regimes, and the mystique of aerospace technology, the market for LLLT devices has expanded into modernity.^{60, 61} A variety of device types are available for LLLT from hand-held laser combs to helmet-like devices.^{60, 61} These devices often use combination laser diodes with LEDs, operating at red or near-infrared (NIR) wavelengths (around 650 nm).⁶¹ Many are FDA-cleared for sale within the United States; however, evidence of their efficacy remains inconclusive.⁶²

MECHANISM OF ACTION

The photobiomodulation effect underlying improved hair growth, though not fully elucidated, is believed to follow a three-step approach that covers actions at the mitochondrial, cellular, and tissue levels.^{58, 63} First, cytochrome oxidase C, the most likely endogenous chromophore for LLLT, absorbs red or NIR light which stimulates production of adenosine triphosphate (ATP) and release of nitric oxide (NO) by the mitochondrial respiratory chain, as well as suppression of reactive oxygen species (ROS).^{58, 63} Next, redox-related cellular signaling is activated by mobilized ATP and NO, which regulates inflammatory, migratory, and proliferatory responses.^{58, 63} Finally, activated cells contribute to anagen re-entry by hair follicles, through improved microvascular circulation, cell cycling, and reduced inflammation.^{58, 63}

The photobiomodulation effect does not occur across all energy fluences.⁶⁴ In fact, laser fluences below a minimum threshold do not stimulate cellular activity, while too-high fluences can lead to activity suppression and eventually cell death.⁶⁴ Most LLLT devices operate at a fluence of 2-5 J/cm²; however, the optimal dose likely varies between devices, functional wavelengths, and skin types.⁶⁵

EFFICACY

The efficacy of LLLT for treatment of AGA is still under investigation. According to recent-meta analyses of randomized controlled trials, LLLT significantly increases hair

density and hair diameter in AGA patients.^{60, 66, 67} However, these same meta-analyses acknowledge limitations present within their included clinical trials; namely, there is a lack of large-scale randomized clinical trials, a range of devices and parameters are grouped together, a measured risk of bias is present among included studies, and some studies have “a clear relation with the industry.”^{60, 66, 67} Therefore, further large-scale, independent studies may be required to verify the efficacy of these devices.

Factors that have been shown to significantly increase hair density improvements with LLLT are total duration of treatment exposure (including duration of irradiation session and number of sessions per week), distance to scalp, and using a laser diode-only device.^{61, 68} Lasers are more collimated and less divergent compared to light emitted by LEDs.⁶⁹ Although laser diodes are more favorable to targeted transmission of light, they are more expensive than LEDs, which likely underlies manufacturer preference for combination laser-LED devices.⁶¹

SAFETY

Clinical trials studying LLLT treatment of AGA report minimal side effects related to the intervention.^{60, 66, 67} Of the studies that do report adverse events, common complaints include headache, pruritus, paresthesia, and eczema.^{60, 66, 67} In general, LLLT is regarded as a safe, well-tolerated treatment for AGA.

Fractional level laser therapy

HISTORY AND APPROVAL STATUS

Since the 1960's, innovation of laser technology has coincided with studies on the potential medical applications of these devices.⁷⁰ In the 90's, laser therapy became standard treatment hair removal, skin resurfacing, and rejuvenation.⁷⁰ Fractional laser technology first emerged in the early 2000's, which allowed for fine-tuned control and improved safety in the treatment of various dermatological conditions relative to the earlier non-fractional lasers.⁷¹ While non-fractional lasers irradiate the entire area of exposed skin, fractional lasers split the laser beam into many “spots,” creating microthermal zones (MTZs) within the skin.⁷¹ This preserves the tissue architecture surrounding targeted areas.⁷¹

Clinical trials beginning in the early 2010's have investigated the utility of fractional laser technology in the management of AGA by two methods. The first is laser-assisted drug delivery (LADD); an approach to improve the permeability of topical medications through the creation

of MTZs in skin.⁷² The second method is fractional laser monotherapy; direct laser stimulation of the hair follicle and surrounding tissue to facilitate hair growth in AGA patients.⁷³ Currently, no fractional laser protocols are FDA-approved for the treatment of alopecia.⁷⁴

MECHANISM OF ACTION

The ablative fractional lasers used in the treatment of AGA include the erbium-doped yttrium aluminum garnet laser (Er:YAG), erbium-doped glass laser (Er:glass) and fractional carbon dioxide laser (FCO₂).⁷⁵ These lasers target water chromophores in the dermal layers, leading to vaporization of tissue within MTZs and epithelial remodeling.⁷⁶

With respect to LADD for AGA, creation of MTZs with fractional lasers allows for greater dermal penetration of topical hair loss treatments, including minoxidil, platelet-rich plasma (PRP), and growth factors.⁷² By enhancing medication absorption, LADD leads to increased exposure of the hair follicle and surrounding tissue to medication, supporting their beneficial influences on hair growth.⁷²

With respect to fractional laser monotherapy for AGA, stimulation of the body's natural repair processes is believed to be the primary driver of improved hair growth.⁷⁷ In particular, increased microvascularization in response to tissue ablation increases blood flow to the hair follicle, enhancing oxygen and nutrient availability.⁷⁷ This effect is secondary to expression of growth factors, including vascular endothelial growth factor (VEGF), keratinocyte growth factor (KGF), and tumor growth factor beta-1 (TGF-β1), as well as modulation of the inflammatory microenvironment.⁷⁸ Laser stimulation may also directly induce hair follicle anagen growth through increased Wnt/β-catenin signaling and activation of hair follicle stem cells (HFSCs).^{78, 79}

EFFICACY

As of yet, there is insubstantial evidence to determine whether fractional lasers are an effective tool in the treatment of AGA. The technique is relatively new; the majority of clinical trials are from the last ten years and are varied in their device type, treatment protocol, and concomitant therapies.⁷⁵

In theory, LADD is likely to offer improved hair growth if it can, at best, increase bioavailability of proven AGA drugs such as topical minoxidil.^{72, 80, 81} Two clinical trials investigating LADD with topical 5% minoxidil, one using FCO₂ and the other using Er:glass laser, have reported increased hair density and hair shaft diameter compared to minoxidil monotherapy.^{80, 81}

A recent meta-analysis compared the outcomes of eight

studies investigating fractional laser combination (LADD) and monotherapy in treating AGA.⁷³ When combination and monotherapies were aggregated, the authors report a significant improvement in hair diameter with FCO₂ and Er:glass lasers, but no improvements in hair density.⁷³ The same effects were found upon separate analysis of four monotherapy studies.⁷³ The results of the analyses are limited by a paucity of high-quality studies, lack of double-blinding procedures, and a measured risk of bias among included trials.^{73, 75} Additionally, the authors note that improvements in hair shaft diameter found in these studies were not durable, and regressed within months of treatment discontinuation.⁷³

SAFETY

Fractional lasers represent a safe, well-tolerated treatment for AGA that, similar to LLLT, limits patient exposure to systemic medications. Side effects reported in clinical trials are few and mild in nature.⁷³ Among these, transient erythema, burning sensations, itching, and scaling are common.⁷³

Platelet-rich plasma

HISTORY AND APPROVAL STATUS

Platelet-rich plasma (PRP) is an autologous platelet solution which is prepared by centrifugation of a small volume of patient blood.⁸² When activated by thrombin, calcium, or mechanical agitation, alpha granules within platelets release high concentrations of growth factors into solution.⁸³ Descriptions of PRP can be found as early as 1975; however, its first documented clinical application was to counteract hemodilution prior to open-heart surgery in 1987.⁸⁴ It has since been implemented in orthopedics, dentistry, dermatology, and gynecology among other medical specializations.⁸⁴

Currently, PRP does not have FDA-approval as a treatment for AGA; however, certain devices used to prepare PRP have been "cleared" via the FDA 510(k) pathway.^{85, 86} Therefore, the use of PRP as a biologic drug is considered off-label, which means its use in AGA is not substantiated by sound scientific evidence and has led to lack of standardization in protocols among practitioners.^{85, 86}

MECHANISM OF ACTION

While the precise mechanism of hair growth promotion by PRP has not been fully elucidated, various contributory factors have been proposed.

Recent studies have demonstrated a proliferatory and anti-apoptotic effect of PRP on follicle dermal papillae

(DP) cells due to stimulation by growth factors.^{87, 88} Activated PRP has high growth factor concentrations, including epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factor-1 (IGF-1), transforming growth factor- β (TGF- β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), which are known to regulate cell proliferation, differentiation, and migration.^{87, 88} These effects may be in part due to induction of the Wnt/ β -catenin signaling pathway, which elongates the anagen phase of the hair follicle.⁸⁷

PRP is also believed to promote a microenvironment around the hair follicle conducive to growth. Hair growth induction by PRP treatment has been shown to be correlated with angiogenesis in a mouse model.⁸⁹ Additionally, TGF- β released by alpha granules is known to modulate inflammation surrounding the hair follicle.⁸⁷

EFFICACY

As mentioned above, evidence of efficacy of PRP use in AGA has suffered from lack of standardization and optimization of treatment protocols. Further, there have been relatively few high-quality, randomized controlled trials to systematically review; nevertheless, recent meta-analyses have investigated the available clinical trials.^{90, 91} These analyses show that PRP clinical trials report significant increases in both hair density and hair thickness compared to control conditions.^{90, 91} While number of PRP treatments and amount injected per treatment does not appear to have an impact, factors that improve treatment success include younger age and frequent application.⁹⁰

SAFETY

Clinical trials investigating PRP use in AGA have not reported serious adverse events related to treatment.⁹¹ Minor effects related to the subdermal application of PRP include pain, erythema, edema, headaches, pinpoint bleeding, and scalp sensitivity.⁹¹

PRP monotherapy avoids potential systemic side effects of mainstay AGA drug regimens and risk of drug-drug interactions, which is an attractive benefit to patients and practitioners alike.⁹² In addition, the autologous nature of PRP poses little risk of immunogenic reaction.⁹² As such, PRP may represent a relatively safe therapeutic option for AGA patients.

Microneedling

HISTORY AND APPROVAL STATUS

Microneedling, originally developed for skin rejuvenation, has gained attention as a potential treatment for

male AGA.⁹³ As of 2024, microneedling has been explored off-label for AGA treatment. It may be used as monotherapy or in combination with topical treatments for AGA.⁹⁴

MECHANISM OF ACTION

Microneedling works on the principle of inducing controlled micro-injuries to the scalp by repeated, multi-directional, and sequential movements using fine needles, typically between 0.5 to 3.5 millimeters in length.⁹⁵ These micro-injuries stimulate the release of growth factors, promote increased blood circulation to the hair follicles, and initiate wound healing mechanisms.⁹⁵ This process is believed to enhance the absorption and efficacy of topical medications, such as minoxidil or platelet-rich plasma (PRP), often used concomitantly with microneedling.⁹⁴

EFFICACY

Microneedling has proven effective for male androgenetic alopecia (AGA), with clinical studies reporting notable improvements in hair growth. Patients undergoing microneedling experienced an increase in hair density and hair shaft thickness, with significant improvements observed in a majority of treated individuals.⁹⁶ The intervals between each session varied, and typically ranged from 1-4 weeks.⁹⁵ In one study, after three sessions of microneedling over six months, patients demonstrated a 36.64% and 35.10% increase in frontal and vertex median density and a 9.75% and 9.08% increase in hair shaft diameter in the front and vertex.⁹⁷ Additionally, when combined with 5% minoxidil, microneedling resulted in a significantly greater increase in hair density and diameter compared to either treatment alone.⁹⁸ This combined approach also led to upregulation of key hair growth-related molecules, such as β -catenin, highlighting the potential of microneedling as a possible therapeutic option for AGA.⁹⁸ Further studies are required to establish the role of microneedling in treating AGA.

SAFETY

Microneedling is generally considered safe when performed by trained professionals using sterile equipment. Common side effects include mild erythema and temporary discomfort or pain during or after the procedure.⁹⁴ Adverse events such as infection or scarring are rare but possible, particularly with improper technique or inadequate post-procedural care.⁹⁴

Mesotherapy

HISTORY AND APPROVAL STATUS

Mesotherapy, a technique involving the administration of lower doses of therapeutic agents and bioactive substances via intradermal injections, was first conceptualized in the latter half of the 20th century.^{99, 100} The method was originally intended for pain management and later adapted for cosmetic dermatology, including skin rejuvenation and hair growth treatments.⁹⁹ The technique allows for the localized delivery of drugs, potentially improving efficacy and patient compliance by reducing systemic exposure.¹⁰¹ However, mesotherapy remains unapproved by regulatory bodies like the U.S. FDA and Health Canada for hair loss treatment, primarily due to the lack of standardized protocols and consistent results.^{99, 100}

MECHANISM OF ACTION

Mesotherapy works by injecting therapeutic agents directly into the dermal layer of the skin.¹⁰² This localized approach enhances the bioavailability of the agents by increasing their residence time at the target site, thus potentially improving treatment outcomes.^{99, 100} The technique allows for the use of lower doses compared to systemic administration, reducing the risk of systemic side effects and increasing patient compliance. The direct delivery to the scalp can also bypass barriers faced by topical treatments, such as poor penetration or degradation before reaching the target area.^{100, 101}

EFFICACY

The efficacy of mesotherapy with various agents, including dutasteride, minoxidil, growth factors, botulinum toxin A, stem cells, and multivitamins have been explored in various studies.^{99, 100} Results indicated several significant improvements in hair growth, particularly with the use of minoxidil, dutasteride, and botulinum toxin A.^{99, 100} For example, minoxidil, an FDA-approved treatment for hair loss, showed improved efficacy when delivered via mesotherapy compared to topical applications alone.¹⁰³ Combinations of agents, such as dutasteride with biotin and other supplements, also demonstrated enhanced outcomes.^{48, 104} However, the diversity in treatment regimens, including variations in agent concentration, injection frequency, and session duration, highlights the need for standardized protocols to fully assess mesotherapy's efficacy.

SAFETY

The safety profile of mesotherapy is generally favorable, with most reported adverse effects being mild and tran-

sient. Common side effects include headache, injection site pain, itching, redness, and swelling.⁹⁹⁻¹⁰¹ Serious adverse effects, such as hair loss at the injection site, edema, and even scalp melanoma or frontal fibrosing alopecia, have been reported but are less common.^{105, 106} In many cases the causality of the adverse event to mesotherapy remains uncertain. These severe reactions could be influenced by factors such as hypersensitivity to the injected agents, pre-existing skin conditions, or potential contamination of the preparations used.¹⁰⁰ Given these risks, it is crucial to conduct thorough patient evaluations and consider allergy testing before initiating treatment. Further large-scale randomized, controlled studies are necessary to establish a comprehensive safety profile and to address the potential risks associated with mesotherapy.

Botulinum toxin

HISTORY AND APPROVAL STATUS

Botulinum toxin, widely recognized for its cosmetic applications in wrinkle reduction, has recently been investigated as a treatment for AGA.¹⁰⁷ The exploration of this treatment began in the early 2010s, with initial studies suggesting potential benefits in promoting hair regrowth. However, as of now, botulinum toxin is not officially approved by major regulatory agencies specifically for AGA. Its use for treating AGA remains off-label with ongoing research and clinical trials seeking to better define its role in hair restoration.¹⁰⁷

MECHANISM OF ACTION

The exact mechanism by which botulinum toxin might influence hair growth is not completely understood, but several theories have been proposed.¹⁰⁸ The toxin's ability to block acetylcholine release at neuromuscular junctions may alter the scalp's microenvironment, potentially impacting hair follicle activity.¹⁰⁹ Additionally, by reducing scalp muscle contraction, botulinum toxin might decrease mechanical stress on hair follicles, creating a more favorable environment for hair growth.¹⁰⁷ Some studies also suggest that the toxin could improve blood circulation in the scalp, enhancing nourishment to hair follicles, and its potential anti-inflammatory effects might reduce scalp inflammation, which is often associated with hair loss.^{107, 109, 110}

EFFICACY

Clinical studies on the efficacy of botulinum toxin for AGA have produced promising but variable results.^{107, 108} For in-

stance, a 2020 study reported that 60% of patients experienced a significant increase in hair density, with an average increase of 20–25 hairs per square centimeter after three treatment sessions.¹⁰⁹ Another trial found that 50% of patients showed improvement in hair thickness and overall hair coverage within 6 months of treatment.^{110, 111} The effects are generally temporary, with benefits lasting around 3 to 6 months, necessitating repeated treatments to sustain results. However, the response to treatment can vary based on factors such as the severity of hair loss, the specific formulation of botulinum toxin used, and individual patient characteristics.^{107, 108}

SAFETY

Regarding safety, botulinum toxin is usually well-tolerated.⁵⁶ Common side effects include localized pain, bruising, and mild swelling at the injection site, which are typically short-lived.^{108, 109, 111} Systemic side effects may occur rarely, and there is a small risk of the toxin spreading beyond the intended area, potentially causing unintended muscle weakness.¹⁰⁸ Since the use of botulinum toxin for AGA is relatively recent, its long-term safety profile is not fully established, and ongoing research is crucial to confirm its safety over extended periods.

Stem cells/exosomes

HISTORY AND APPROVAL STATUS

Exosomes – a type of extracellular vesicle (EV) – is an emerging, investigative treatment modality for various dermatological conditions from AGA to wound healing and skin rejuvenation.¹¹² Ever since the start of EV research during the 1980s to 1990s,¹¹³ there has been an exponential expansion of the EV field in the past two decades. This has transformed our understanding of EVs from mere “cellular waste disposal” to a wide range of applications in regenerative medicine, not limited only to treatments but also as diagnostic and prognostic markers.

Exosomes treatment is still in its early developmental stages and a clear regulatory framework has not been proposed to date. None of the marketed exosome products have received regulatory approval. Per the U.S. FDA, exosomes are classified as a biologic under the jurisdiction of the Center for Biologics Evaluation and Research.¹¹⁴ In Europe, EMA considers exosomes as either biologics or Advanced Therapeutic Medicinal Product (ATMP) depending on its content.¹¹⁴ Although there are selected exosome products that received the Investigation New Drug (IND) designation by the USA FDA, direct-to-consumer marketing of such products is not permitted.

MECHANISM OF ACTION

Exosomes are nanoscaled extracellular vesicles that deliver “messages” or cargos from cell-to-cell protected by its lipid bilayer. Through the releasing of its intracellular content (*e.g.*, proteins, lipids, RNAs), exosomes can mediate paracrine signaling between epithelial cells and mesenchymal cells during the hair growth cycle. For instance, exosomes derived from dermal papilla cells containing microRNAs were shown to upregulate the Wnt/ β -catenin pathway leading to an increase in hair growth based on mice model and ex vivo hair follicle culture experiments.¹¹⁵ Due to current technical limitations, the precise mechanism of action of exosomes have not been defined. Exosomes are highly diverse depending on its cellular origin; as well, isolation and purification techniques, culture conditions and storage conditions can affect the quantity and qualitative of exosomes.¹¹⁶

EFFICACY

Exosomes research has mostly remained in the pre-clinical phase with scarce evidence on its efficacy. In a case-series, exosomes sourced from adipose-derived stem cells were administered topically with microneedling in 39 AGA patients.¹¹⁷ After once-weekly applications for 12 weeks, statistically significant improvements in hair density (121.7 to 146.6 hairs/cm²) and thickness (52.6 to 61.4 μ m) were reported.¹¹⁷ In another similar study, topical exosomes treatment derived from adipose stem cells combined with microneedling was administered in 30 AGA patients.¹¹⁸ After 10 treatment sessions, authors reported a statistically significant increase in hair density (161.9 to 166.13 hairs/cm²).¹¹⁸

SAFETY

The USA FDA has issued consumer alerts and warning letters to businesses regarding exosome products.¹¹⁹ Without adhering to Good Manufacturing Practices, exosomes can pose serious safety risks to consumers. Thus far, reports on the topical administrations of exosomes have indicated mild and self-limiting application site reactions such as erythema and itching.^{117, 118} However, injection or infusion of exosomes is illegal in the USA.¹¹⁹ Clinicians are cautioned against administering exosomes, and are advised to avoid making unverified claims.¹¹⁹

Hair transplantation options

Hair transplantation, specifically follicular unit transplantation (FUT) and follicular unit excision (FUE), is an effective treatment for androgenetic alopecia (AGA),

leveraging the patient's own hair follicles to restore lost hair.¹²⁰⁻¹²² These methods are supported by clinical evidence demonstrating their ability to improve hair density and coverage in affected individuals. Both methods aim to address the thinning and baldness associated with AGA by relocating healthy hair follicles from donor areas to areas affected by hair loss.^{122, 123}

FUT

HISTORY AND APPROVAL STATUS

FUT is one of the earliest methods used for hair restoration and has a well-established history.¹²⁴ FUT involves removing a strip of scalp from the donor area, dissecting it into individual follicular units, and then transplanting these units to the recipient area. The technique has been extensively studied and is one of the gold standards for treating androgenetic alopecia. Despite its long history, FUT is an effective option, especially for patients seeking a larger number of grafts in a single session.^{121, 122, 124}

MECHANISM OF ACTION

FUT involves excising a strip of hair-bearing skin from the donor area, typically the back of the scalp. This strip is then dissected into smaller follicular units under a microscope. The donor area is closed with sutures, which results in a linear scar that can be concealed by existing hair.¹²⁴ The individual follicular units are then transplanted into small incisions made in the recipient area. This method allows for the transplantation of a large number of grafts, making it suitable for patients with extensive hair loss or those requiring significant coverage.^{124, 125}

EFFICACY

FUT has proven to be highly effective in treating androgenetic alopecia. It offers the advantage of harvesting a large number of grafts in one session. Clinical studies and patient reviews indicate that FUT can achieve natural-looking and satisfactory results, with improvements in hair density and coverage becoming evident within 6-12 months.¹²⁴

SAFETY

FUT is a generally safe procedure with a well-established safety profile. However, it is associated with a linear scar in the donor area, which can be noticeable if the patient has short hair.^{122, 124, 126} Other potential risks include infection, delayed wound healing, and temporary numbness in the donor and recipient areas. Postoperative care and following the surgeon's instructions are crucial to mini-

mizing these risks.¹²⁴ The overall safety of FUT has been confirmed through numerous studies and clinical practice, and it remains a reliable option for hair restoration.

FUE

HISTORY AND APPROVAL STATUS

FUE is a relatively modern technique in the realm of hair restoration.¹²⁶ It emerged in the early 2000s as an advancement over the traditional FUT method, addressing some of its limitations such as linear scarring.^{127, 128} FUE involves the extraction of individual follicular units from the donor area, which are then transplanted to the balding regions. FUE has gained wide acceptance due to its minimally invasive nature and the reduced risk of noticeable scarring.¹²⁹

MECHANISM OF ACTION

The FUE technique involves the precise extraction of individual hair follicles using a small, circular punch tool. The procedure begins with the donor area being shaved to allow for easier access to hair follicles.^{128, 130} A micro-punch is used to create tiny circular incisions around each follicular unit. These follicles are then gently extracted and prepared for transplantation. The prepared follicles are subsequently implanted into tiny incisions made in the recipient area, where they will continue to grow and integrate with the existing hair.^{129, 131} This method allows for the preservation of natural hair growth patterns and reduces the appearance of scarring.

EFFICACY

FUE has demonstrated significant efficacy in treating androgenetic alopecia. Studies and clinical experience show that FUE can yield natural-looking results with high patient satisfaction.^{122, 127, 129} The success of the procedure largely depends on the skill of the surgeon and the density of the donor hair. Most patients experience a noticeable improvement in hair density and coverage after a few months, with full results becoming evident within 12-18 months.^{122, 129} The effectiveness of FUE is supported by numerous case studies and patient testimonials, which report successful outcomes in terms of both aesthetic improvement and satisfaction.^{122, 129}

SAFETY

FUE is considered a safe procedure with a low risk of complications. The minimally invasive nature of FUE

typically results in a quicker recovery time compared to FUT.^{126, 127, 129} Common side effects include minor swelling, redness, and temporary numbness in the donor and recipient areas. These effects generally resolve within a few days to weeks. The risk of infection is minimal, and scarring is typically limited to small, dot-like scars that are often inconspicuous.^{129, 131} However, it is crucial to choose a qualified and experienced surgeon to minimize risks and ensure optimal outcomes.

Natural products

Overview

Natural medicinal products, often referred to as nutraceuticals, for the treatment of AGA have been growing in popularity in recent years.¹³² Patients may be increasingly seeking natural solutions to their AGA treatment due to medication failures, side-effects associated with traditional pharmaceuticals, or drug contraindications among other reasons.¹³³ It is of note that because these natural products are marketed as supplements, they are regulated by the FDA but are not subject to the same rigor of clinical testing that pharmaceuticals undergo.¹³⁴ It is for this reason that practitioners and patients alike should approach claims of treatment efficacy with skepticism. Nevertheless, we discuss here seven nutraceutical products that have been evaluated by at least one randomized controlled trial (RCT). We have previously reviewed these products using the same inclusion criteria to assess the potential efficacy of these nutraceuticals within the constraints of high-quality clinical testing.¹³⁵

Procyanidins

Procyanidins are a variety of flavonoid compounds that are derived from multiple plant sources.¹³⁶ Type B procyanidins, which are abundant in apples, grapes, and blueberries, represent the most-studied group of these compounds in AGA treatment.¹³⁶ Procyanidins are strong antioxidants and have been suggested to support the proliferation of follicular bulge cells and induce anagen cycling.¹³⁷

Caffeine

Caffeine is a naturally occurring stimulant found in coffee, tea, and cocoa.¹³⁸ Caffeine has been shown to inhibit the activity of 5 α -reductase and phosphodiesterase (PDE) activity, which stimulates a variety of cell types within the hair follicle architecture.¹³⁹

Oryza sativa bran

Rice (*Oryza sativa*) bran is the major by-product of rice milling.¹⁴⁰ Rice bran extract has a high concentration of phytosterols, which are known to inhibit 5 α -reductase activity.¹⁴⁰

Pumpkin seed oil

Pumpkins (*Curcubita pepo*) are winter squashes that are native to South and Central America.¹⁴¹ Pumpkin seed oil has a high concentration of phytosterols, which are known to inhibit 5 α -reductase activity.¹⁴²

Rosemary oil

Rosemary (*Rosmarinus officinalis*) is a house plant and herb that has a long history in folk medicine.¹⁴³ Rosemary oil is commonly added to hair tonics and lotions with claims to stimulate hair growth. It has been shown to inhibit 5 α -reductase activity.¹⁴⁴

Saw palmetto

Saw palmetto (*Serenoa repens*), native to the southeastern USA and West Indies, is a small palm that has been used in traditional medicines.¹⁴⁵ Saw palmetto has been shown to inhibit 5 α -reductase activity.¹⁴⁶

Watercress

Watercress (*Nasturtium officinale*) is an aquatic flowering plant with origins in Europe and Asia.¹⁴⁷ The mechanism of action of watercress extract in AGA is less clear, but beneficial effects¹⁴⁷ have been suggested to be mediated through activation of mitogen-activated protein kinase (MAPK) receptors or Wnt signalling.^{148, 149}

A statement on evidence

While natural products are often promoted as treatments for AGA, there may be a lack of robust scientific evidence to support their efficacy. Most studies on natural remedies are small, poorly controlled, or lack rigorous methodologies. While some ingredients have shown potential in preliminary research, their effects are not comparable to clinically approved treatments like minoxidil or finasteride. Therefore, while natural products may offer anecdotal benefits, they should not be relied upon as primary treatments for AGA without further high-quality evidence regarding short-term and long-term efficacy and side-effects profile.

Conclusions

Our article explores current and emerging therapies for male AGA. We recommend starting with topical minoxidil and oral finasteride, as they are well-studied and FDA-approved treatments for male AGA. If these treatments are ineffective or unsuitable due to potential side effects, clinicians may consider alternative options as appropriate.

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Conflicts of interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions

Aditya K. Gupta contributed to the conceptualization of the manuscript. The methodology was developed by Aditya K. Gupta and Mesbah Talukder, while resources were provided by Aditya K. Gupta. The original draft of the manuscript was prepared by Mesbah Talukder, Shruthi Polla Ravi, Daniel Taylor and Tong Wang and Aditya K. Gupta participated in the review and editing process. All authors read and approved the final version of the manuscript.

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