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Topical solutions for androgenetic alopecia: evaluating efficacy and safety

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ABSTRACT

Androgenetic alopecia (AGA) presents a significant challenge in clinical practice due to its prevalence and impact on patients' quality of life. With a diverse array of available treatment options, selecting the most appropriate therapy demands careful consideration of factors such as efficacy, safety, practicality, and cost. This review aims to evaluate the efficacy and safety profiles of various topical treatments for AGA, investigating their potential advantages in limiting systemic side effects compared to oral medications. This article explores the pharmacology, mechanisms of action, clinical efficacy, and adverse events associated with topical medications like minoxidil, finasteride, ketoconazole shampoo, clascoterone, latanoprost, spironolactone, flutamide, cetirizine, pyrilutamide, and GT20029.

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Keywords: androgenetic alopecia, topical, treatment, minoxidil, finasteride, clascoterone

INTRODUCTION

Androgenetic alopecia (AGA) is a common dermatologic condition that, while not life-threatening, often leads to considerable distress and negatively impacts patients' quality of life (QOL). It is thought to be caused by androgens in genetically predisposed men and women [1, 2]. As individuals age, the prevalence of AGA increases and affects approximately 50% of older men and 15% of postmenopausal women [3]. It poses a formidable challenge for clinicians in treatment selection. Factors such as efficacy, side effect profiles, practicality, and cost demand meticulous consideration, further complicated by the absence of standardized grading techniques and the diverse array of available treatment options. In men, AGA typically manifests as frontal recession and vertex thinning, while female-pattern hair loss (FPHL) is characterized by reduced hair density over the crown without frontal hairline involvement [4, 5]. Hair follicles are affected mainly through the local transformation of testosterone into more potent dihydrotestosterone (DHT) by type II 5α-reductase in androgen-sensitive dermal papilla cells [6]. Finasteride, a 5α-reductase inhibitor that blocks the conversion of testosterone into DHT, is a Food and Drug Administration (FDA)-approved treatment for AGA. While its effectiveness is well-established, some research reports an array of adverse side effects, often referred to as "post-finasteride syndrome", that can develop in some patients treated with oral finasteride and sometimes persist even after discontinuing the medication [7, 8]. Hence the topical application of finasteride has been investigated in hopes of providing a similar reduction in scalp DHT levels while having less of a systemic effect. Similarly, an oral version of FDA-approved medication minoxidil seems to be as effective as the topical application [9], however, reported side-effects such as electrocardiogram (ECG) changes (tachycardia, t-wave changes, preventricular contractions), postural hypotension, dizziness, pericardial effusion, lower limb oedema, and hypertrichosis seem to make oral administration of minoxidil less desirable [10]. It appears that topical treatments for AGA might be a sensible route of treatment, provided they may offer similar effectiveness while presenting with fewer side effects. This paper aims to assess the efficacy and safety profiles of topical medications

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in the management of AGA, with a specific emphasis on their potential to limit systemic side effects. This analysis seeks to provide clinicians and researchers with valuable insights into the emerging therapeutic landscape of AGA, highlighting possible new treatment options and facilitating informed decision-making and optimizing patient care.

MINOXIDIL

Topical minoxidil is an FDA-approved treatment for AGA and has been widely prescribed for this condition for several decades. It has also been used off-label for other hair disorders such as scarring alopecia, alopecia areata (AA), chemotherapy-induced alopecia and others, as well as a beard and eyebrow enhancement. Minoxidil was first developed for the treatment of hypertension and the commonly observed side-effect of hypertrichosis led to its topical form use in hair growth stimulation. It is available on the market in different forms, such as foam, shampoo and solutions.

The main active metabolite is minoxidil sulfate, conversion to which is higher in hair follicles than the surrounding skin. It is thought to bind to adenosine triphosphate (ATP) sensitive potassium channels causing smooth muscle relaxation, which is generally proposed to contribute to its hypotensive effect. Relaxation of blood vessels results in increased blood flow and a greater supply of oxygen and nutrients to the hair follicle. Production of vascular endothelial growth factor (VEGF), a potent vasodilator, stimulator of angiogenesis and a multifunctional growth factor is also increased [11]. Minoxidil is also hypothesized to cause an anti-inflammatory effect, reducing perifollicular microinflammation [12–14]. Topical application of 3% minoxidil solution resulted in increased anagen hair count and decreased the count of hair in the telogen phase in AGA patients [15].

Multiple studies have demonstrated minoxidil's effectiveness in promoting hair growth. In a 12-month observational study on 904 male patients with AGA treated with 5% minoxidil solution applied twice daily, the affected region has been reported to significantly decrease in 62% of eligible patients and has become larger in only 2.9% of subjects. 84.3% of patients reported hair regrowth of various degrees [16]. In a 48-week randomized controlled trial (RCT) on 352 males with AGA, 5% minoxidil solution produced 45% more hair regrowth than the 2% solution at the end of the study. An earlier response to treatment was also noted, with a non-vellus hair count at 8 weeks equivalent to that of a 16-week treatment with 2% minoxidil. Both concentrations were well tolerated with no evidence of systemic effects [17]. Side effects with topical minoxidil use include irritant and allergic contact dermatitis, scalp irritation, pruritus and facial hypertrichosis, which present more often with higher per cent formulations [18].

TOPICAL FINASTERIDE

5α-reductase is an enzyme responsible for converting testosterone into the more potent DHT. Hair follicles are primarily impacted by the local conversion of testosterone to DHT through the action of type II 5α-reductase in androgen-sensitive dermal papilla cells. Finasteride, a type II 5α-reductase inhibitor, blocks the conversion to DHT and minimizes androgen-mediated follicle miniaturization. Oral finasteride has been approved by the FDA for male-pattern hair loss since 1997. Although it remains a topic of debate, a growing body of research recognizes a consistent range of side effects linked to finasteride use, commonly referred to as "post-finasteride syndrome" [19]. This syndrome includes sexual dysfunction, decreased libido, and gynecomastia [8, 20, 21]. While these symptoms typically resolve after discontinuing the medication, they can sometimes persist for three months or longer and may even lead to depression and suicidal thoughts [7]. This issue has sparked interest in topical finasteride application in hopes of reducing its adverse systemic effects while providing a local therapeutic effect in AGA patients.

Topical finasteride is usually applied as 1% topical finasteride gel or 0.25% finasteride spray, applied twice daily to the scalp. Its effects on hair regrowth and reduction of balding were first reported by Mazzarella et al. [22] in 1997 in a 16-month placebo-controlled trial of 52 patients. In a phase III randomized, controlled clinical trial of 458 patients hair count in a targeted area was significantly improved compared to placebo, and the improvement was similar to that of oral finasteride. At the same time, the reduction in mean serum DHT concentrations was lower with topical *vs.* oral finasteride (34.5% *vs.* 55.6%), indicating a lesser chance of sexual side effects related to a decrease in systemic DHT. There were no serious side effects related to the treatment [23]. Another study on 40 male patients treated with a topical solution of 0.25% finasteride mixed with 3% minoxidil versus 3% minoxidil solution alone, reported superior effects on hair diameter and density compared to 3% minoxidil. No systemic adverse events or sexual dysfunction were reported [24]. A randomized controlled trial on 45 male patients, found no significant difference in therapeutic effect between 1% finasteride gel and 1 mg finasteride tablets and a significant difference in hair count and terminal hair count in both groups. Potential side effects of topical finasteride include contact dermatitis, skin erythema, increased liver enzymes, nocturnal enuresis, testicular pain, headaches, presyncope, and oropharyngeal pain [25].

KETOCONAZOLE SHAMPOO

Ketoconazole is an imidazole derivative with antifungal and anti-inflammatory properties, used in the treatment of seborrheic dermatitis. In addition, ketoconazole has

antiandrogenic properties, inhibiting testosterone synthesis and consequently diminishing DHT levels. This multifaceted pharmacological profile supports its theoretical viability in the treatment of AGA. A systematic review of ketoconazole for AGA treatment which included 5 human studies supports the potential efficacy of ketoconazole shampoo in AGA treatment [26]. Three of those studies evaluated the impact of ketoconazole on hair shaft diameter, a critical parameter in AGA characterized by hair follicle miniaturization [27]. An increase in hair shaft diameter [28, 29] and the pilary index (a measure combining per cent anagen phase and diameter) [29] was reported. Clinical improvements in AGA, as evidenced by photographic evaluation, were also noted [30]. Additionally, two studies investigated the effect of ketoconazole shampoo on hair density, yielding conflicting results. One study reported an increase in hair density, [29] while the other found no significant change [28]. While most studies utilized a 2% formulation, one human study employed 1% ketoconazole shampoo [28]. The frequency of treatment varied from twice weekly to daily use, with positive outcomes even with the least frequent application of 2–3 times per week [30]. Notably, topical ketoconazole demonstrated a favourable safety profile since there were no significant side effects associated with treatment. Considering this, ketoconazole might be an alternative or adjuvant therapy in the treatment of AGA. Further large-scale prospective trials are warranted to establish its definitive role in AGA management and to better understand its mechanism of action.

CLASCOTERONE

Clascoterone is a novel androgen antagonist and the first topical antiandrogen approved by the FDA for the treatment of acne vulgaris. Clascoterone seems to effectively inhibit androgen receptor (AR) regulated transcription, comparable to the performance of the 5α-reductase inhibitor, finasteride. Furthermore, clascoterone demonstrates superior efficacy over enzalutamide, a direct AR-antagonist, in inhibiting interleukin-6 (IL-6) synthesis in DHT-stimulated cells [31]. By blocking DHT-induced signalling pathways and cytokine production, clascoterone may mitigate hair follicle miniaturization. Its unique mechanism of action involves competitively binding with AR, antagonizing DHT, and reducing dermal inflammation. This profile distinguishes clascoterone from existing therapies for AGA. In the Phase II exploratory study involving 70 adult male subjects with AGA, clascoterone demonstrated superior efficacy compared to cyproterone acetate or 17α-estradiol across various measures, including scalp sebometric measurement, hair shaft diameter, hair follicle density, and pull test/wash test. In a Phase II proof-of-concept (POC) study on 73 patients, clascoterone exhibited superior (39%) improvements in target area hair count (TAHC) changes compared to the vehicle group (16%). Its efficacy was similar to that of minoxidil (36%) [32]. In a phase II dose-ranging clinical trial involving 344 male subjects, patients applied various concentrations of Clascoterone solution or vehicle twice daily for 12 months. Significant improvements in hair count were seen across all Clascoterone groups compared to the vehicle, with the highest improvement in the Clascoterone 7.5% solution group. More patients in the Clascoterone groups experienced increased hair growth compared to the vehicle [33]. Phase II trials conducted in acne patients did not reveal indications of systemic effects [34]. However, further research, including large-scale clinical trials, is warranted to validate its efficacy and safety profile in AGA management.

LATANOPROST

Latanoprost, a prostaglandin F2α analogue initially employed for glaucoma treatment, garnered attention for its potential in addressing alopecia following observations of eyebrow and eyelash growth in glaucoma patients [35]. Latanoprost was reported to extend the anagen phase of the hair cycle, which indicated it might be a viable option for mitigating hair loss [36]. In a double-blinded, placebo-controlled clinical trial involving 16 male patients with mild AGA, latanoprost 0.1% and placebo were applied daily for 24 weeks on separate scalp areas. Results showed a significant increase in hair density on the Latanoprost-treated site compared to the baseline and the placebo-treated site at the end of the study [37]. These findings suggest the effectiveness of Latanoprost in increasing hair density. However, further trials are necessary to evaluate its efficacy and safety profile.

TOPICAL SPIRONOLACTONE

Spironolactone, a potassium-sparing diuretic, also exhibits antiandrogenic effects. It blocks the AR in target tissues, which is often used by dermatologists to diminish the effects of testosterone on skin and hair such as FPHL, acne, and hirsutism, especially in female patients [38]. Recent trials have explored the efficacy of topical spironolactone for the treatment of AGA, yielding promising results. One RCT on 60 patients (39 male, 21 female) found that 1% spironolactone gel led to clinical improvement in 80% of patients after 12 months. When used alone, spironolactone gel showed significant improvement, with even better results seen when combined with 5% minoxidil [39]. Another non-randomized comparative study involving 40 patients applying a solution containing 5% spironolactone and 5% minoxidil reported a decrease in vellus hair and an increase in upright regrowing hair compared to 5% minoxidil solution alone, over a 12-week period [40]. These findings indicate that topical spironolactone may effectively treat AGA, either alone or in combination with minoxidil. Although some adverse effects

like contact dermatitis and dizziness were reported in a few patients, overall, those using only topical spironolactone gel experienced minimal and tolerable side effects, with no impact on libido or sexual performance. Further trials are warranted to validate the efficacy and safety of topical spironolactone, particularly in larger and more diverse patient populations.

TOPICAL FLUTAMIDE

An emerging possibility for promoting hair growth is topical flutamide, a nonsteroidal anti-androgen. Unlike its systemic administration, which can lead to adverse systemic effects such as decreased libido, topical application seems to offer a safer route, especially in the treatment of skin disorders. In an experimental model of human scalp skin graft transplanted onto severe combined immune deficient (SCID) mice, comparing topical formulations of flutamide and finasteride for AGA, flutamide demonstrated superior efficacy in enlarging hair follicles. Topical flutamide gel significantly increased hair length, diameter, and the number of hairs per graft, surpassing the effects of the vehicle alone. Histological examination supported these findings, showing more hairs in the growth phase with flutamide treatment, indicating its ability to reverse alopecia. Plasma monitoring revealed no systemic effects of flutamide, suggesting its localized action [41]. In a randomized, double-blinded clinical trial involving 40 patients with AGA, combination therapy with 2% topical flutamide and 5% minoxidil was compared to 5% minoxidil alone. The results showed that topical flutamide combined with a minoxidil solution was significantly more effective in increasing hair density, hair thickness, and patient satisfaction compared to the minoxidil-only group [42]. These findings suggest that topical flutamide has potential as a treatment for AGA. However, further research, including prolonged studies with a larger cohort and exploration of different vehicles, is needed to better evaluate the efficacy and safety profile of topical flutamide.

TOPICAL CETIRIZINE

Topical cetirizine, an antihistamine medication, has shown encouraging potential for treating hair loss, particularly AGA in both male and female patients. A 24-week RCT including 66 female patients with AGA compared topical cetirizine and minoxidil *vs.* minoxidil and placebo. The study reported a significant increase from baseline in frontal and vertex terminal and vellus hair density with a significant improvement in vertex hair shaft thickness and average number of hairs per follicular unit. Furthermore, patient self-assessment scores favoured the cetirizine group, indicating a higher satisfaction level. Notably, the study reported no significant difference in side effects between the cetirizine and minoxidil groups, suggesting a favourable safety profile for cetirizine [43]. Another study on 40 male patients, compared 1% topical cetirizine *vs.* 5% minoxidil, revealing a notable increase in total and vellus hair density after 16 weeks of treatment. An increase in the percentage of hair in the anagen phase in both groups was also reported. Although minoxidil demonstrated superior results, cetirizine exhibited effectiveness without adverse reactions, making it a promising alternative for male AGA treatment [44]. In a 6-month study involving 60 female patients, while minoxidil showed greater efficacy in terms of hair density, cetirizine still provided favourable therapeutic effects, particularly for patients who cannot tolerate minoxidil [45]. These findings underscore the potential of topical cetirizine as a safe and effective alternative for hair loss treatment.

TOPICAL PYRILUTAMIDE

KX-826, previously known as pyrilutamide, is a topical drug that blocks the signalling pathway of AR when applied locally to peripheral skin tissue. By reducing the sensitivity of AR to androgens in the pilosebaceous gland, it aims to limit systemic side effects. It is being developed in tincture and gel forms as a potential first-in-class treatment for AGA and acne vulgaris. Phase II trials for male and female AGA in China have shown promising results, with significant improvements in non-vellus TAHC observed after 24 weeks of treatment with KX-826. The safety profile was favourable, with no serious adverse events reported [46]. The ongoing clinical trials are focused on evaluating its efficacy and safety for treating AGA in male adults in China. Notably, a 1.0% tincture formulation is being tested, which has shown increased retention and concentration on scalp cells compared to the 0.5% tincture used in prior studies, suggesting a potential for enhanced clinical efficacy [47]. KX-826 has undergone multiple successful clinical trials in both China and the US, demonstrating a promising safety profile and effectiveness for both male and female AGA patients. The recently concluded Phase II trial in the US indicated significant improvements in hair growth with a dose-response relationship observed, particularly with the 0.5% twice daily dosage [48]. Following these encouraging results, Kintor Pharma is preparing for a Phase III trial in the US. Concurrently, a long-term safety trial is underway in China to further assess the prolonged use of KX-826, involving 270 participants over a 52-week period [49]. These trials aim to solidify the drug's safety and efficacy profile, ultimately supporting its use as a long-term treatment for AGA.

GT20029

GT20029, developed using Kintor Pharma's proprietary Proteolysis Targeting Chimera (PROTAC) platform, works by targeting AR proteins for degradation, acting locally to

avoid systemic exposure and reduce androgen sensitivity in hair follicles and sebaceous glands. Studies in DHT-induced mouse models demonstrated significant hair growth promotion, while trials on testosterone propionate-induced skin hamster flank organ acne models showed inhibition of flank organ enlargement. Phase I clinical trials in China and the US showed good safety, tolerability, and pharmacokinetics [50]. Recently, the China phase II clinical trial for treating male AGA reached its primary endpoint, demonstrating statistically significant and clinically meaningful results with good safety and tolerability. This multi-centre, randomized, double-blind, placebo-controlled study involved 180 male AGA patients and evaluated the efficacy and safety of GT20029 in 0.5% and 1% dosages administered once daily (QD) or twice weekly (BIW). The trial results indicated a significant increase in non-vellus TAHC compared to placebo, with the 0.5% QD group showing an increase of 16.80 hairs/cm^2 from baseline and the 1% BIW group showing an increase of 11.94 hairs/cm^2. No adverse sexual effects were observed, and the incidence of other adverse events was comparable to the placebo [51]. Based on these results, the company plans to initiate a phase III clinical trial in China and a phase II clinical trial in the U.S. Additionally, a phase II trial for acne treatment is also in preparation.

DISCUSSION

Currently, there are numerous treatments for AGA available, including oral and topical medications, hormonal therapies, laser therapy, mesotherapy, microneedling, platelet-rich plasma (PRP), and surgical procedures of hair transplantation. Nonetheless, treating AGA remains particularly challenging due to the variability in patient response to conventional therapies as well as the incomplete understanding of the condition's pathogenesis. Topical minoxidil, oral finasteride, and low-level laser therapy (LLLT) are the only treatments for AGA approved by the FDA, all of which may be effective in treating patients. However, patients must adhere to lifelong therapy as AGA continues to progress if treatment is discontinued, highlighting the importance of side effect profile consideration.

This review aimed to evaluate the efficacy and safety profiles of various topical treatments for AGA, emphasizing their potential to limit systemic side effects compared to oral counterparts. The findings indicate that topical treatments offer a promising alternative to oral medications, combining effective management of AGA with a reduced risk of systemic adverse effects (Tab. 1). By delivering medication directly to the affected area, these treatments can limit systemic absorption and reduce the risk of systemic side effects. For instance, topical minoxidil has been shown to effectively promote hair growth with localized side effects such as irritant and allergic contact dermatitis, pruritus, and facial hypertrichosis. Similarly, topical finasteride is gaining traction as a viable alternative to its oral counterpart. By applying finasteride directly to the scalp, patients can mitigate the risk of systemic absorption and associated side effects, such as sexual dysfunction, which are more commonly reported with oral administration. Studies indicate that topical finasteride maintains comparable efficacy to oral forms in reducing hair loss and promoting regrowth while offering a better safety profile.

Ketoconazole, primarily an antifungal agent, also reduces scalp inflammation and inhibits DHT production, benefiting hair density and thickness in AGA patients. Clascoterone, a newer topical anti-androgen, prevents DHT from binding to hair follicle receptors, showing promising results in improving hair count and density. Emerging treatments like topical spironolactone, flutamide, cetirizine, pyrilutamide and GT20029 have shown varying degrees of efficacy in clinical trials. These treatments may offer additional options for patients, particularly those who may not tolerate minoxidil or finasteride. Topical spironolactone, for instance, has demonstrated significant improvements in hair density and thickness with a minimal side effect profile, making it a valuable alternative for patients with AGA.

Although the results with topical treatments are encouraging, current research is limited by sample size, study design, and measurement techniques. Future research should focus on larger, long-term studies with standardized metrics and comprehensive safety monitoring to better evaluate the efficacy and safety of these treatments. Further exploration should provide more insight into the effectiveness of different treatments across diverse patient populations and varying degrees of AGA, potentially offering a safer and more tolerable approach for patients. The diversity of topical agents available also allows for personalized treatment plans, addressing individual patient needs and preferences.

CONCLUSIONS

The evaluation of various topical treatments for AGA highlights their potential as effective and safer alternatives to oral medications. Topical minoxidil and finasteride have robust evidence supporting their efficacy and favourable safety profiles, making them mainstays in AGA management. Emerging treatments such as clascoterone, spironolactone, and other topical agents show promise and warrant further investigation.

Topical treatments offer several advantages, including localized action (Fig. 1), reduced systemic absorption, and fewer systemic side effects. These benefits are particularly important given the chronic nature of AGA and the need for

Table 1. Efficacy, safety and mechanism of action of various topical treatment options in AGA

Treatment	Mechanism of action	Formulation	Main findings	Adverse events
Minoxidil	Increases blood flow, increases VEGF, anti-inflammatory	Foam, shampoo, solution (2%, 5%)	Significant hair regrowth, higher efficacy with 5% solution	Contact dermatitis, scalp irritation, pruritus, facial hypertrichosis
Topical finasteride	Inhibits type II 5α-reductase, reduces DHT levels	Gel (1%), spray (0.25%)	Efficacy comparable to oral finasteride, lower systemic DHT reduction	Contact dermatitis, skin erythema, increased liver enzymes, nocturnal enuresis, testicular pain, headaches, presyncope, oropharyngeal pain
Ketoconazole	Anti-inflammatory, reduces androgen synthesis	Shampoo (1%, 2%)	Increase in hair shaft diameter, potential improvement in hair density	Oiliness/dryness of the hair and scalp; discolouration, irritation of the scalp
Clascoterone	AR inhibition, anti-inflammatory	Cream (1%), solution (up to 7.5%)	Superior efficacy in hair count improvement, comparable to minoxidil	Erythema, pruritus, dryness, telangiectasia
Latanoprost	PGF2α analogue prolongs the anagen phase of the hair cycle	Solution (0.1%)	Increase in hair density	Further trials are needed for the safety profile
Topical spironolactone	AR inhibition	Gel (1%), solution (5%)	Significant improvement in hair growth, decrease in vellus hair and increase in upright regrowing hair, especially when combined with minoxidil	Contact dermatitis, dizziness
Topical flutamide	AR inhibition	Gel (2%)	Increased hair density and thickness, more effective in combination with minoxidil	No systemic effects reported
Topical cetirizine	Antihistamine, anti-inflammatory	Solution (1%)	Increased hair density, effective for both male and female AGA	No significant side effects reported
Topical pyrilutamide (KX-826)	AR inhibition	Tincture (0.5%, 1%), gel	Significant improvement in hair count, favourable safety profile	Itching, dryness, redness, contact dermatitis
GT20029	AR degradation	Tincture (0.5%, 1%)	Significant hair count improvement, good safety and tolerability	Itching, dryness, redness

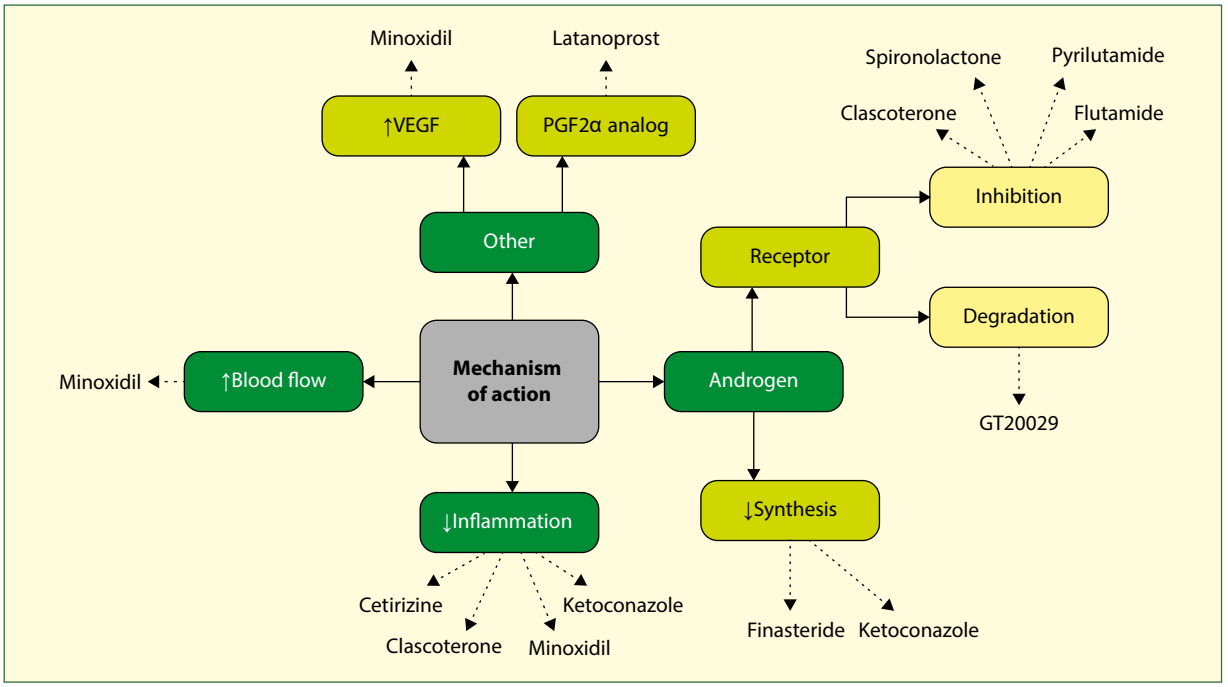

Figure 1. Mechanism of action of various topical hair loss medications

long-term treatment adherence. Clinicians should consider these factors when selecting appropriate therapies for their patients, balancing efficacy with safety to optimize outcomes.

Future research should focus on large-scale, long-term clinical trials to further validate the efficacy and safety of emerging topical treatments. Additionally, exploring combination therapies and understanding the mechanisms of action will enhance the therapeutic landscape of AGA, providing more comprehensive and individualized patient care.

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Conceptualization, investigation, visualization, writing: original draft — MK; conceptualization, writing: review and editing — OS.

Conflict of interest

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