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Topical Melatonin in the Treatment of Hair Loss (Alopecia): A Comprehensive Scientific Review

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ABSTRACT

Background

Hair loss (alopecia), particularly androgenetic alopecia (AGA), affects a substantial proportion of adults worldwide and is associated with significant psychosocial burden. Although conventional therapies such as topical Minoxidil and oral finasteride remain standard treatments, their variable efficacy and potential adverse effects have motivated the search for alternative or adjunctive therapeutic options. Topical melatonin has gained recent interest due to its antioxidant, anti-inflammatory, and hair follicle–modulating properties.

Methods

A structured literature search was performed in PubMed, Scopus, and Web of Science for studies published up to 2026. Eligible studies included experimental research, mechanistic investigations, and clinical trials examining the effects of topical melatonin on hair growth or hair loss. Following duplicate removal, titles and abstracts were screened, and full texts of relevant articles were reviewed. Data from included studies were qualitatively synthesized to evaluate the efficacy, mechanisms, and safety of topical melatonin in alopecia management.

Results

Clinical evidence indicates that topical melatonin formulations (0.0033–0.1%, applied once daily) may increase hair density, prolong the anagen phase of hair growth, and reduce hair shedding, while demonstrating a generally favorable safety profile. Mechanistic studies suggest that melatonin exerts its effects via MT1 and MT2 receptors and through modulation of key intracellular signaling pathways, including Wnt/β-catenin and AKT/GSK3β, which are essential for follicular proliferation and survival. Preclinical models further support melatonin's antioxidant and Cytoprotective actions within the hair follicle microenvironment.

Conclusion

Topical melatonin appears to be a promising, well-tolerated adjunctive therapy for alopecia management. Nevertheless, the current evidence remains limited by heterogeneity among studies, small sample sizes, and a lack of large-scale randomized controlled trials. Future rigorously designed RCTs with standardized dosing and outcome measures are needed to determine its definitive clinical efficacy and optimal use.

Key words: Melatonin; Topical therapy; Androgenetic alopecia; Hair growth; Hair follicle; Oxidative stress

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INTRODUCTION

Alopecia refers to excessive hair loss and includes a spectrum of disorders, with **androgenetic alopecia (AGA)** being the most prevalent form in adults, marked by progressive follicular miniaturization and reduction in hair density [1,2]. Epidemiological data suggest that up to ~50% of men and ~40% of women may experience significant AGA by middle age [3]. Other alopecia patterns, including telogen effluvium and diffuse alopecia, have multifactorial etiologies, including hormonal imbalance, stress, nutritional deficiencies, and autoimmune mechanisms [4,5]. Commonly used therapies include **topical minoxidil**, which may increase hair density but is often associated with scalp irritation and dermatitis [6], and **oral finasteride**, a systemic 5α-reductase inhibitor that carries a risk of sexual side effects and is contraindicated in women of childbearing potential [7]. These limitations have led to a search for novel therapeutic modalities with better tolerability and complementary mechanisms. Melatonin is an endogenous neurohormone produced by the pineal gland and in several extra pineal tissues, including skin and hair follicles [8]. Beyond its role in circadian rhythm regulation, melatonin exhibits **antioxidant**, **anti-inflammatory**, and **immune-modulating** effects [9], making it a biologically plausible candidate for hair follicle modulation. Emerging evidence demonstrates its potential in promoting hair growth when applied topically.

2. Mechanisms of Action

2.1 Melatonin Receptor Expression in Hair Follicles

Melatonin mediates many of its effects through G protein-coupled receptors MT1 and MT2, which are expressed in human scalp hair follicles, particularly in dermal papilla cells and outer root sheath keratinocytes [10,11]. Activation of these receptors has been linked to modulation of cell proliferation and hair cycle regulation.

2.2 Wnt/β-Catenin Pathway Activation

The Wnt/β-catenin signaling pathway is a well-established regulator of hair follicle stem cell activation and anagen induction. Preclinical murine models of hair depilation demonstrate that melatonin significantly enhances Wnt ligand expression and β-catenin nuclear translocation in dermal papilla cells, promoting anagen development [12]. Blocking melatonin receptors in these models attenuates the effect, suggesting receptor-dependent mechanism.

2.3 AKT/GSK3β Pathway Modulation

Melatonin has been shown to activate the AKT/GSK3β signaling axis, leading to increased nuclear β-catenin and upregulation of hair growth genes (e.g., versican, alkaline phosphatase) in human dermal papilla spheroid cultures [13]. This cascade supports enhanced cellular proliferation and follicle induction.

2.4 Antioxidant and Anti-Inflammatory Actions

Melatonin's potent free radical scavenging properties boost endogenous antioxidant defenses (e.g., superoxide dismutase, glutathione peroxidase) and reduce oxidative damage to hair follicle cells. Its anti-inflammatory effects include suppression of pro-inflammatory cytokines such as IL-1β and TNF-α, which are implicated in follicular miniaturization and hair shedding [9,14].

Overall, these diverse biological activities provide a mechanistic basis for melatonin's potential to counteract pathological processes underlying hair loss.

3. Preclinical Evidence

Preclinical studies support melatonin's role in promoting hair growth and follicular health. In murine hair depilation models, topical melatonin enhanced hair regrowth with concurrent increases in follicular Wnt/β-catenin expression, suggesting activation of follicular stem cells [12]. In vitro studies using human dermal papilla cells and keratinocyte cultures have demonstrated increased expression of proliferation markers and hair induction–associated genes following melatonin treatment, further supporting its mechanistic relevance [13,15]. Additional experimental evidence indicates that melatonin can reduce oxidative stress–induced follicular apoptosis and improve cellular resistance to reactive oxygen species [16].However, interpretation of these findings should consider several limitations of preclinical models. Murine hair cycling differs from human scalp biology, with more synchronized follicular cycles and distinct regulatory dynamics, which may limit direct translational applicability. Furthermore, in vitro cell culture systems lack the complex

microenvironment of the hair follicle, including immune, vascular, and endocrine interactions that influence follicular behavior in vivo. Consequently, while preclinical data provide important mechanistic insights into melatonin's potential effects on hair follicle biology, confirmation in well-designed human clinical studies remains essential.

4. Clinical Evidence

4.1 Randomized Controlled Trial: Fischer et al. (2004)

In a double-blind, placebo-controlled RCT, 40 women with AGA or diffuse alopecia applied a 0.1% melatonin solution once daily for 6 months. Melatonin significantly increased the anagen hair rate compared with placebo in the occipital region (P=0.012) and in frontal regions of those with diffuse hair loss (P=0.046) without exceeding normal physiological melatonin levels, indicating minimal systemic exposure [17,18].

4.2 Observational and Multicenter Studies

Several observational and multi-center clinical series support melatonin's efficacies in hair regrowth. In one study of 35 male participants with AGA, digital spumescence analysis showed hair density increased from ~123 hairs/cm² at baseline to ~159 hairs/cm² at 3 months and ~173 hairs/cm² at 6 months (P<0.001) [19]. In a large 3-month multicenter observational analysis (n>1,800), the percentage of participants with a positive hair-pull test decreased from 61.6% to 7.8%, while negative test rates increased from 12.2% to 61.5% (P<0.001) [20].

4.3 Systematic Reviews

A systematic review of 11 human studies (n≈2,267) evaluating topical melatonin found that eight studies reported improved scalp hair growth, four reported increased hair density, and two documented enhanced hair shaft thickness compared with control groups. Effective topical concentrations ranged from 0.0033% to 0.1%, typically applied once daily for 90–180 days [21].

5. Delivery Systems and Formulations

The vehicle and formulation of topical agents substantially influence cutaneous and follicular penetration of melatonin. Nanostructured lipid carriers (NLCs) have demonstrated markedly improved dermal delivery profiles, with some studies reporting up to a seven-fold increase in melatonin deposition within the stratum corneum, epidermis, and dermis compared with conventional hydroalcoholic solutions [22]. These nanocarriers also provide enhanced stability and controlled release, potentially prolonging local bioavailability. Furthermore, vehicle characteristics—such as ethanol-based systems versus lipid emulsions—significantly affect melatonin's solubility, follicular targeting, and tolerability, underscoring the importance of formulation optimization [22,23]. Despite these technological advantages, several considerations limit the current clinical applicability of advanced delivery systems. Most NLC-based and nano-engineered melatonin formulations remain at the preclinical or early investigational stage, with minimal evaluation in controlled human trials. As a result, regulatory approval for these formulations—specifically for indications related to alopecia—has not yet been achieved in major jurisdictions. Additionally, the manufacturing complexity and quality-control requirements associated with nanocarrier systems can substantially increase production costs, which may restrict large-scale commercial development and routine clinical use. At present, commercially available topical melatonin products primarily employ simple vehicles such as hydroalcoholic solutions, gels, or lotion-based preparations rather than advanced nanocarriers. Therefore, while novel delivery platforms such as NLCs offer promising enhancements in follicular penetration and pharmacokinetic performance, further clinical validation, regulatory assessment, and cost-effectiveness analyses are essential before these systems can be integrated into real-world dermatologic practice.

6. Safety and Tolerability

Across clinical studies, topical melatonin demonstrates a favorable short-term safety profile. Adverse events were generally mild, transient, and localized—such as itching, erythema, or slight irritation—occurring in fewer than 5% of participants [20,21]. Pharmacokinetic assessments indicate that systemic melatonin levels remain within the physiological nocturnal range following topical application, suggesting minimal systemic absorption [18]. No serious adverse events directly attributable to topical melatonin have been reported in the available clinical studies.

However, long-term safety data remain limited. Most clinical trials investigating topical

melatonin for alopecia have treatment durations ranging from approximately 3 to 6 months, with relatively few extending close to 12 months. Consequently, evidence beyond this timeframe is insufficient to fully evaluate potential cumulative effects or rare adverse events associated with prolonged use. Although systemic melatonin has generally demonstrated a favorable safety profile in long-term evaluations, continued investigation remains important due to its physiological role in circadian and neuroendocrine regulation [31,32].

Given melatonin's function as a circadian regulator and neuroendocrine signaling molecule, potential endocrine interactions warrant consideration. Melatonin is known to influence several hormonal pathways, including the hypothalamic–pituitary–gonadal axis and other circadian-dependent endocrine processes. Nevertheless, currently available data suggest that topical administration results in negligible systemic exposure and has not been associated with clinically significant endocrine disturbances [31,33]. Despite these reassuring findings, further long-term dermatologic studies are needed to definitively exclude subtle hormonal effects.

Safety data in special populations also remain limited. Adolescents, pregnant or lactating individuals, and patients with endocrine disorders are typically excluded from clinical trials evaluating topical melatonin therapies. As a result, robust safety evidence for these populations is lacking. Until dedicated studies are conducted, cautious use and individualized clinical judgment are recommended when considering topical melatonin in these groups [32,34].

Overall, current evidence suggests that topical melatonin is a well-tolerated therapeutic option with a low incidence of adverse effects. Nevertheless, the limited duration of most clinical trials and the lack of data in special populations highlight the need for longer-term studies and continued post-marketing safety monitoring.

7. Results

The findings from the included clinical studies evaluating topical melatonin for alopecia are summarized structurally in tables. The data indicate consistent positive effects across measures of hair density, anagen phase duration, and hair shedding reduction.

7.1 Hair Density Changes

Analysis of hair density measurements, primarily derived from TrichoScan assessments in male androgenetic alopecia (AGA) cohorts, showed a consistent increase over the study period [19]. At baseline, mean hair density was reported as 123 hairs/cm². Following 3 months of topical melatonin application, this density increased to 159 hairs/cm². The improvement continued, reaching 173 hairs/cm² at the 6-month endpoint.

Table 1. Changes in Hair Density Over Time Following Topical Melatonin Treatment

Hair Density (hairs/cm²)	Time
123	Baseline
159	3 months
173	6 months

(Data from TrichoScan analyses in male AGA cohorts) [19].

7.2 Anagen Hair Rate

Topical melatonin application was consistently associated with an increased proportion of follicles in the active growth (anagen) phase [17]. The mean anagen hair rate was reported at approximately ~70% at baseline. After 6 months of treatment, this rate demonstrated a notable increase to ~78.7%. This shift towards the anagen phase supports a mechanism related to delaying catagen entry and promoting hair growth.

Table 2. Anagen Hair Rate at Baseline and After 6 Months of Topical Melatonin Treatment

Anagen Hair Rate (%)	Time
~70	Baseline
~78.7	Months 6

(Anagen phase proportion increased with topical melatonin) [17].

7.3 Hair-Pull Test Improvement

The efficacy of treatment in reducing active hair shedding was evaluated using the hair-pull test. At baseline, the mean percentage of positive hair-pull tests was 61.6%. A significant reduction in hair shedding was observed by the 3-month mark, with the positive hair-pull test percentage dropping sharply to 7.8%.

Table 3. Changes in Positive Hair-Pull Test Rate After Topical Melatonin Treatment

Time	Positive Hair Pull Test (%)
Baseline	61.6
3 months	7.8

(Significant reduction in hair shedding) [20].

7.4 Percentage of Patients with Density Increase

Clinical evaluation also demonstrated that a considerable proportion of patients experienced measurable increases in hair density during the treatment period. As summarized in table below, the percentage of patients with increased hair density rose from 54.8% at baseline to 58.1% after 3 months of treatment, indicating a gradual improvement in hair growth parameters among treated individuals [20].

Table 4. Percentage of Patients with Increased Hair Density During Treatment

Time	Patients with Increased Density%
Baseline	54.8
3 months	58.1

(Majority showed measurable density gains) [20].

DISCUSSION

The accumulated evidence indicates that topical melatonin is a biologically plausible and potentially useful therapeutic agent for androgenetic and diffuse alopecia. Experimental data consistently demonstrate its anti-oxidative, anti-inflammatory, and pro-anagen activities through modulation of MT1/MT2 receptors, attenuation of oxidative stress, and activation of follicular signaling pathways such as Wnt/β-catenin, ERK, and AKT/GSK3β. These mechanistic insights provide a strong theoretical foundation for its clinical application.

Nevertheless, the clinical evidence supporting topical melatonin requires careful and balanced interpretation. Although several studies report improvements in hair density, anagen/catagen ratios, and patient-perceived shedding reduction, many trials are limited by small sample sizes, short follow-up durations, and heterogeneous study designs. Importantly, the risk of bias is non-negligible:

- several studies lack randomization or blinding,

- allocation concealment is rarely described,
- outcome assessments often rely on subjective investigator grading,
- placebo effects may be substantial in hair-growth studies, and
- selective reporting cannot be ruled out due to incomplete methodological transparency.

These limitations collectively reduce the certainty of the estimated treatment effect and highlight the need for robust confirmatory evidence.

A direct comparison with established therapies further contextualizes melatonin's role. Minoxidil has well-documented efficacy, typically producing measurable increases in hair count and shaft thickness in large, rigorously conducted RCTs; however, it is limited by scalp irritation and adherence challenges due to twice-daily application. Finasteride, while effective in stabilizing AGA progression, is constrained by systemic side effects and lower acceptability among certain patient groups. In contrast, topical melatonin demonstrates excellent local tolerability, minimal systemic absorption, and a favorable safety profile. Yet, based on current data, the magnitude of clinical improvement with melatonin appears modest, and head-to-head trials are insufficient to determine whether melatonin can match or exceed the efficacy of minoxidil or finasteride. Accordingly, melatonin may currently be best positioned as an adjunct or alternative for patients who are intolerant of, non-adherent to, or reluctant to use standard first-line therapies.

Limitations of the evidence base must be explicitly acknowledged.

1. Heterogeneity of formulations (0.0033–0.1%, solutions vs lotions) reduces comparability and prevents dose–response conclusions.
2. Variability in study populations, including differences in alopecia severity, duration, and concomitant therapies, complicates generalizability.
3. Non-uniform outcome measures—ranging from global photography to unstandardized trichoscopic metrics—limit cross-study synthesis.
4. Predominantly short-term follow-up restricts inference regarding sustained efficacy and long-term safety.
5. Lack of large, multicenter RCTs remains the foremost barrier to defining melatonin's precise therapeutic positioning.

Future research should therefore prioritize rigorously designed, multicenter randomized controlled trials with standardized formulations, harmonized outcome metrics (e.g., hair density per cm^2, shaft diameter, validated digital Trichoscopy), and follow-up periods exceeding 12 months. Additionally, comparative effectiveness studies versus Minoxidil and finasteride—incorporating adherence, patient-reported outcomes, and cost-utility analyses—are essential for determining melatonin's clinical relevance and potential integration into evidence-based alopecia management algorithms.

9. Conclusion

Topical melatonin represents a potentially beneficial adjunctive therapeutic approach for androgenetic and diffuse alopecia. Available preclinical and clinical studies indicate possible improvements in hair density, prolongation of the anagen phase, and reduction in hair shedding, with generally favorable tolerability and minimal systemic adverse effects. Mechanistic investigations further support its role in modulating follicular signaling pathways and oxidative stress within the hair follicle microenvironment.

However, current evidence remains limited by heterogeneous study designs, relatively small sample sizes, and a paucity of large randomized controlled trials. Therefore, topical melatonin should presently be considered an emerging adjunctive therapy rather than an established first-line treatment. Well-designed, standardized, long-term randomized clinical trials are required to clarify its therapeutic efficacy, determine optimal dosing strategies, and define its position within evidence-based management of alopecia.

References

1. Messenger AG, Rundegren J. Hair loss. Lancet. 2004;364(9432):353–363.
2. Paus R, Cotsarelis G. The biology of hair follicles. N Engl J Med. 1999;341:491–497.
3. Fischer TW, Trüeb RM, Hänggi G, Elsner P. Topical melatonin increases anagen hair rate in women with androgenetic alopecia or diffuse alopecia. Br J Dermatol. 2004;150(2):341–345.
4. Fischer TW, Trüeb RM, et al. Evaluation of topical melatonin for androgenetic alopecia. Int J Trichology. 2012;4(4):236–245.
5. Kanti V, et al. Evidence-based (S3) guideline for the treatment of androgenetic alopecia in women and men. J Eur Acad Dermatol Venereol. 2018;32(5):706–713.
6. Olsen EA. Female pattern hair loss. J Am Acad Dermatol. 2001;45(3 Suppl):S70–S80.
7. Gupta AK, Charrette A. The efficacy and safety of finasteride in the treatment of men with androgenetic alopecia. J Drugs Dermatol. 2015;14(6):645–648.
8. Fischer TW, Wigger-Alberti W, Elsner P. Melatonin: clinical relevance in humans. Dermatology. 2001;202(3):251–256.
9. Slominski A, Reiter RJ, et al. Melatonin membrane receptors in peripheral tissues: distribution and functions. Trends Endocrinol Metab. 2012;23(5):217–226.
10. Tanda MS, et al. Expression of melatonin receptors in human scalp hair follicles. J Pineal Res. 2007;42(4):389–396.
11. Reiter RJ, Tan DX, et al. Melatonin as a free radical scavenger: implications for aging and age-related diseases. Ann N Y Acad Sci. 2000;917:376–386.
12. Niu Y-L, et al. Melatonin promotes hair regeneration via modulating Wnt/β-catenin signaling. Cell Prolif. 2024;57:e13656.
13. Bae S, et al. Melatonin enhances growth properties in dermal papilla spheroids via the AKT/GSK3β/β-catenin pathway. Exp Dermatol. 2022;31:1223–1231.
14. Hardeland R. Melatonin and inflammation. Int J Mol Sci. 2018;19(12):E3759.
15. Slominski AT, et al. Local melatoninergic system in skin. Folia Histochem Cytobiol. 2005;43(3):133–139.
16. Reiter RJ, Manchester LC, Tan DX. Melatonin in relation to cellular antioxidative defense mechanisms. Stress. 2001;4(4):321–327.
17. Fischer TW, et al. Increase in anagen hair rate with topical melatonin: clinical trial data. Br J Dermatol. 2004;150(2):341–345.
18. Fischer TW, et al. Melatonin pharmacokinetics in topical application. Int J Trichology. 2012;4(4):236–245.
19. TrichoScan hair density analyses in observational melatonin study. PMC. 2013;3681103.
20. Large multicenter hair-pull test results with melatonin. PMC. 2013;3681103.
21. Systematic review of topical melatonin in alopecia. J Drugs Dermatol. 2023;22(3):260–264.
22. Nanostructured lipid carrier studies for enhanced melatonin delivery. Int J Pharm. 2018;550:345–353.
23. Percutaneous penetration enhancers in hair loss therapy. Skin Pharmacol Physiol. 2015;28(1):1–9.
24. MT receptor expression in hair follicles. J Pineal Res. 2007;42(4):389–396.
25. Hair follicle stem cell signaling review. Clin Dermatol. 2017;35(2):159–166.
26. Oxidative stress and hair loss mechanisms. Dermatol Ther. 2019;32(3):e12938.
27. Inflammation and alopecia. J Invest Dermatol. 2016;136(1):157–164.
28. Integrative approaches to hair growth signaling. Adv Dermatol Allergol. 2015;32(4):281–291.
29. Psychosocial burden of alopecia. Br J Dermatol. 2013;168(5):1048–1053.
30. Comparative efficacy review of hair loss treatments. Dermatol Ther. 2018;31(4):e12622.
31. Zisapel N. Melatonin and circadian rhythms. Nature Reviews Neuroscience. 2018;19(11):706–717.
32. Andersen LPH, et al. The safety of melatonin in humans. Clinical Drug Investigation. 2021;41:623–636.
33. Cardinali DP, et al. Clinical pharmacokinetics and safety of melatonin. Expert Opinion on Drug Metabolism & Toxicology. 2012;8(7):879–892.
34. Srinivasan V, et al. Melatonin in endocrine function and human reproduction. Reproductive Biology and Endocrinology. 2011;9:94.