

Botanicals In Hair Follicle (HF) Health: Molecular and Cellular Mechanisms of Plant-Derived Compounds in HF Regeneration and Growth

Charit Seneviratne, PhD
AlviArmani Research Institute

Abstract

The human hair follicle is a mini-organ that is generated by the dynamic interaction between epithelial and mesenchymal germinal layers (Ohyama, 2019). And that undergoes cyclic phases of growth (anagen), regression (catagen), and rest (telogen) governed by tightly coordinated molecular signaling network (Duverger & Morasso, 2013). Dysregulation of these networks—particularly those involving Wnt/beta-catenin signaling, Sonic hedgehog (Shh), bone morphogenetic protein (BMP), multitude of growth factors, hormonal pathways including sex hormones, metabolic and prostaglandins, inflammatory cascades, oxidative stress pathways, and microvascular regulation—underlies common forms of hair loss. Conventional pharmacologic therapies typically target single nodes within this network, which may limit efficacy and cause long-term side-effects (Colin-Pierre et al., 2022; Liang et al., 2023).

Plant-derived compounds encompass structurally diverse phytochemical classes capable of modulating multiple signaling pathways simultaneously (Sarkar et al., 2009). Emerging evidence indicates that phytosterols, polyphenols, flavonoids, terpenoids, and alkaloids can influence key molecular regulators of hair follicle cycling, including Wnt pathway activation, inflammatory signaling attenuation, oxidative stress reduction, and angiogenic support.

This review synthesizes current understanding of the molecular regulation of the hair cycle and examines the mechanistic basis by which botanical compounds modulate follicular biology. A basic pharmacologic framework is proposed to describe the multi-target effects of multiple botanical molecules on follicular regeneration. This complex and synergistic molecular modulation of hair follicle cycling represents a biologically coherent approach aligned with the complexity of follicular signaling networks and warrants further investigation through transcriptomic, metabolomic, and systems biology methodologies.

Keywords: hair follicle cycle; Wnt/ β -catenin; Sonic hedgehog; BMP; FGF; oxidative stress; NF-kB; phytochemicals; network pharmacology; systems biology

1. Introduction

The human hair follicle is a highly specialized mini-organ characterized by continuous cycles of growth, regression, and regeneration. These cycles are governed by reciprocal interactions between epidermally-derived multipotent stem cell population called hair follicle stem cells (HFSC) residing in the “bulge region” of the hair follicle (HF) and mesenchymal-derived dermal papilla cells (DPC), forming a dynamic epithelial–mesenchymal interaction that results in the generation and regeneration of a new hair follicle. And the hair follicle morphogenesis and cycling depend on tightly regulated molecular pathways that coordinate cellular proliferation, differentiation, apoptosis, and metabolic activities on multitude of cues such as hormonal; growth factor; neuronal and environmental factors (Hughes et al., 2021).

The main molecular signaling pathways that include, Wnt/ β -catenin, Sonic Hedgehog (Shh), Notch, Noggin, Bone Morphogenetic Protein (BMP) as well as growth factors interact extensively in reciprocal feedback loops to maintain follicular homeostasis and dictate the transition between the cycling phases: anagen, catagen, and telogen (Bellani et al., 2025).

The hair loss disorders arise from the dysregulation within this network often precipitates in the follicular miniaturization and premature transition to the catagen phase, the clinical hallmarks of such pathologies (Bellani et al., 2025; Dincheva et al., 2023). For example, higher sensitivity for Dihydro-Testosterone (DHT), imbalance between pro-inflammatory cytokine to anti-inflammatory cytokines and elevated oxidative stress levels collectively contribute to the progressive degradation of the follicular microenvironment (Joshi et al., 2020).

These pathological factors are further exacerbated by the down-regulation of essential growth factors, such as IGF-1 and VEGF, which are critical for sustaining the longevity of the anagen phase.

Given the multifactorial nature of these disorders, therapeutic strategies that leverage plant derived phytochemicals (Botanicals) to restore this intricate molecular balance have gained significant scientific interest (Bellani et al., 2025). These botanical interventions frequently act by upregulating key pro-growth signals such as Wnt/ β -catenin signaling while concurrently suppressing inhibitory pathways like BMP, thereby re-establishing the regenerative signaling hierarchy (Hu et al., 2021).

Understanding these nuanced regulatory interfaces provides a crucial foundation for evaluating how plant-derived agents may influence the threshold for follicle re-entry into the active growth cycle. In this context, specific phytochemicals found in botanical extracts have demonstrated the ability to inhibit 5α -reductase activity, effectively limiting the conversion of testosterone to dihydrotestosterone and mitigating its suppressive effects on follicle cycling (Liu et al., 2023). Moreover, these phytochemical interventions often modulate the expression of Bax and caspase-3, preventing premature apoptosis and facilitating a prolonged

transition into the catagen phase (Prugsakij et al., 2023). By modulating these pro-apoptotic markers, such compounds effectively preserve the integrity of dermal papilla cells and extend the duration of the proliferative anagen phase. In addition, these pharmacologically active botanicals often stimulate potassium channel opening, mimicking the membrane hyperpolarizing effects of established clinical therapies to sustain follicular metabolism (Prugsakij et al., 2023).

These multifaceted mechanisms highlight how plant-derived bioactive constituents, including phenolic compounds and terpenoids, serve as potent modulators for targeting cell proliferation pathways and enhancing the survival of dermal papilla and hair follicle stem cells. Collectively, these molecular adjustments promote follicular vascularization and cellular differentiation, offering a robust framework for addressing the underlying causes of pathological hair thinning (Choi et al., 2024).

Given the multiplicity of pathways involved, interventions that modulate only a single molecular target which is the typical approach of many conventional pharmaceuticals, may be insufficient for comprehensively addressing the complex etiology of hair loss (Fang et al., 2024).

This review examines the molecular architecture of hair follicle cycling and evaluates the mechanistic basis by which plant-derived compounds influence follicular regeneration through polypharmacological multi-target synergistic modulation of hair follicular cell proliferation and differentiation, thereby offering a more comprehensive strategy for the clinical management of various alopecia phenotypes.

2. Molecular Architecture of Hair Follicle Cycling

2.1 Hair Cycle Phases

The hair follicle undergoes a cyclic process comprising four primary phases: anagen (growth), the longest phase (2-7 years ; about 80-90%), characterized by active proliferation, differentiation, and hair shaft production; catagen (regression), a brief transitional phase lasting 7–21 days in which ~1% of follicles undergo apoptosis-driven involution of the lower compartment; telogen (resting or refractory phase), marked by quiescence and exogen (shedding), during which the old hair is released (Dincheva et al., 2023; SANTOS et al., 2015)

This rhythmic remodeling is orchestrated by the activation of quiescent hair follicle stem cells, which respond to local morphogenic gradients and systemic endocrine signals (Chueh et al., 2013). Anagen initiation is gated by activation of the Wnt/ β -catenin, SHH, Noggin and BMP signaling pathways, critical for initiating stem cell proliferation and differentiation to form new hair shafts (Wang et al., 2022). The dermal papilla, positioned at the base of

the hair follicle, serves as a crucial signaling center, modulating these pathways to dictate the onset and progression of the anagen phase (Fan et al., 2022; Soe et al., 2023). The Wnt/ β -catenin pathway, in particular, plays a pivotal role in the telogen-anagen transition and the maintenance of hair follicle stem cell stemness, with various Wnt ligands stabilizing β -catenin and inducing anagen-phase specific gene expression to promote hair growth and shaft elongation (Fan et al., 2022). Inhibition of BMP signaling further supports anagen onset, as BMP acts antagonistically to Wnt signaling by maintaining follicular quiescence (Schneider et al., 2009). The Wnt/ β -catenin, Sonic hedgehog (SHH), and Notch signaling pathways act synergistically for anagen induction, with their intricate interactions being fundamental to the precise regulation of hair follicle activity (Zhang et al., 2024).

Conversely, catagen transition is triggered by cessation of these mitogenic signals and upregulation of pro-apoptotic factors, inducing controlled regression of the lower follicular compartment (Joshi et al., 2020; Wu et al., 2023). This process is mediated by antagonists such as Dickkopf-1, which inhibits Wnt/ β -catenin signaling to hasten growth phase exit (Dincheva et al., 2023; Leirós et al., 2016). In androgenetic alopecia, crosstalk between androgen receptor and Wnt/ β -catenin pathways aberrantly suppresses Wnt signaling, promoting follicular miniaturization (Dincheva et al., 2023; Joshi et al., 2020). Similarly, the aberrant elevation of BMP signaling serves to enforce follicular quiescence, further preventing the reactivation of stem cells and delaying the necessary transition into the next anagen phase (Bellani et al., 2025). Additionally, the Sonic hedgehog pathway remains essential for orchestrating follicular morphogenesis and the structural maturation of the follicle during the proliferative surge (Bellani et al., 2025; Hu et al., 2021).

2.2 Stem cell Niche and Dermal Papilla Signaling

The interplay between these two compartments is fundamental, for both HF generation and regeneration and growth (Chen et al., 2020). The dermal papilla acts as a signaling hub that interprets external stimuli to regulate the activation, migration, and differentiation of stem cells within the bulge (Vatanashevanopakorn & Sartyoungkul, 2023).

In the adult hair follicle, the hair follicle stem cell (HFSC) niche is primarily localized within the bulge region, where quiescent stem cells are maintained until they receive precise molecular cues to initiate the regenerative cycle (Alves, 2017; Chueh et al., 2013). Activation of these stem cells during the telogen-anagen transition is the most important event in the regenerative cycle, where the formation of the secondary hair germ serves as the primary catalyst for down-growing epithelial cells to differentiate into the new follicular structure (Cotsarelis, 2005). This activation process is fundamentally regulated by the interaction between the mesenchymal dermal papilla and the overlying epithelial stem cells, which facilitate the necessary signaling for follicular outgrowth (Park, 2022; SANTOS et al., 2015). Specifically, dermal papilla cells secrete diverse morphogens, including FGF and BMP lig-

ands, which engage in a spatial competition to regulate the quiescence or proliferation of these progenitor populations (Driskell et al., 2011). Furthermore, the shift from a BMP-dominated inhibitory environment to one characterized by Wnt/ β -catenin activation is essential for prompting these stem cells to exit quiescence and initiate hair matrix regeneration (Colin-Pierre et al., 2022; Leirós et al., 2016). Moreover, the cyclic expression of BMPs in the dermis remains spatially and temporally distinct from the follicular Wnt/ β -catenin cycle, acting as a crucial switch to govern the transition between growth and resting phases (Blanpain & Fuchs, 2009).

Hair Cycle Phases

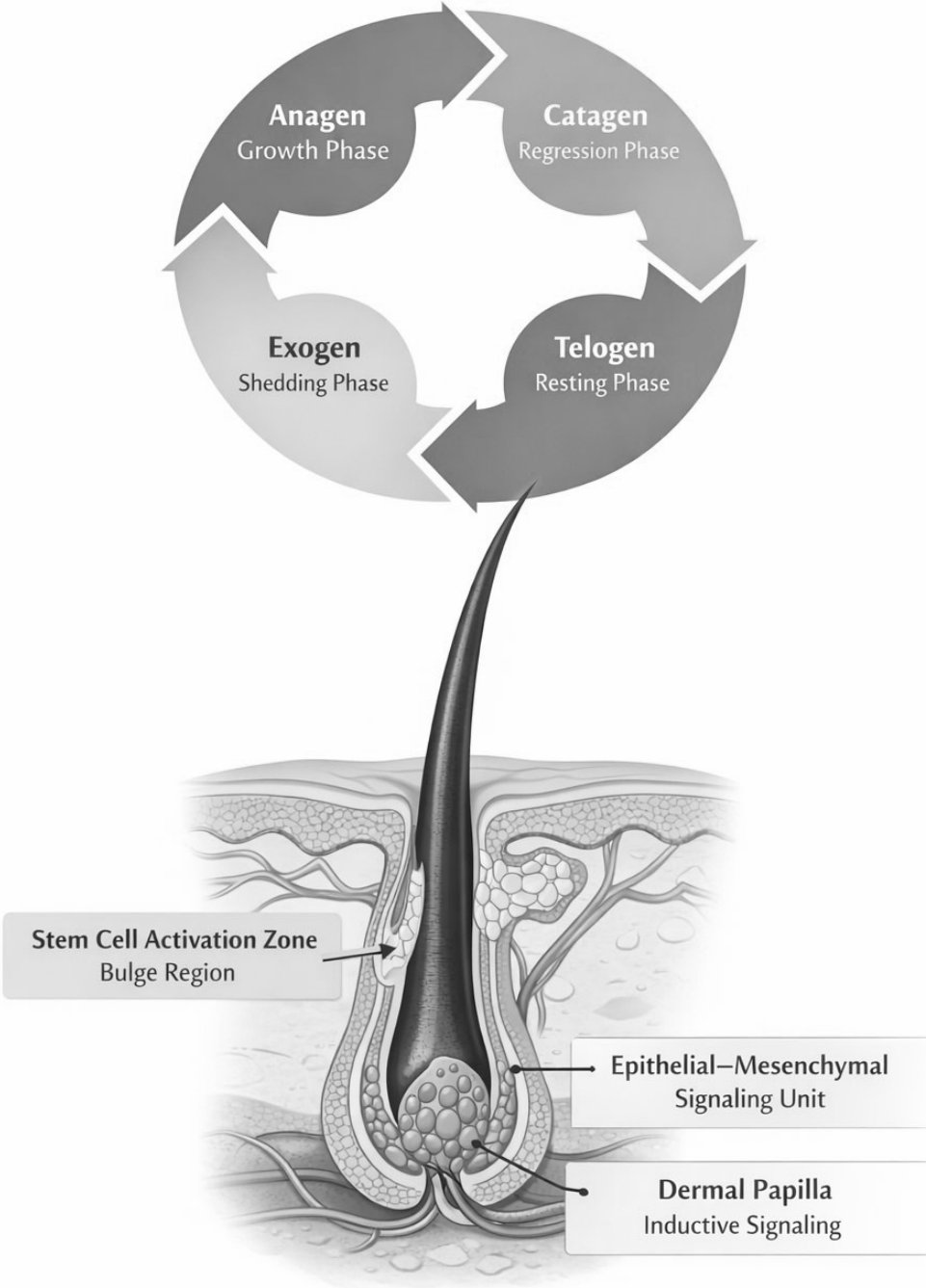


Figure 1: Schematic representation of the hair follicle morphogenesis and cycle, and signaling niche

2.3 Integrated signaling Networks in Follicular Morphogenesis

Molecular Signaling Network of the Hair Follicle

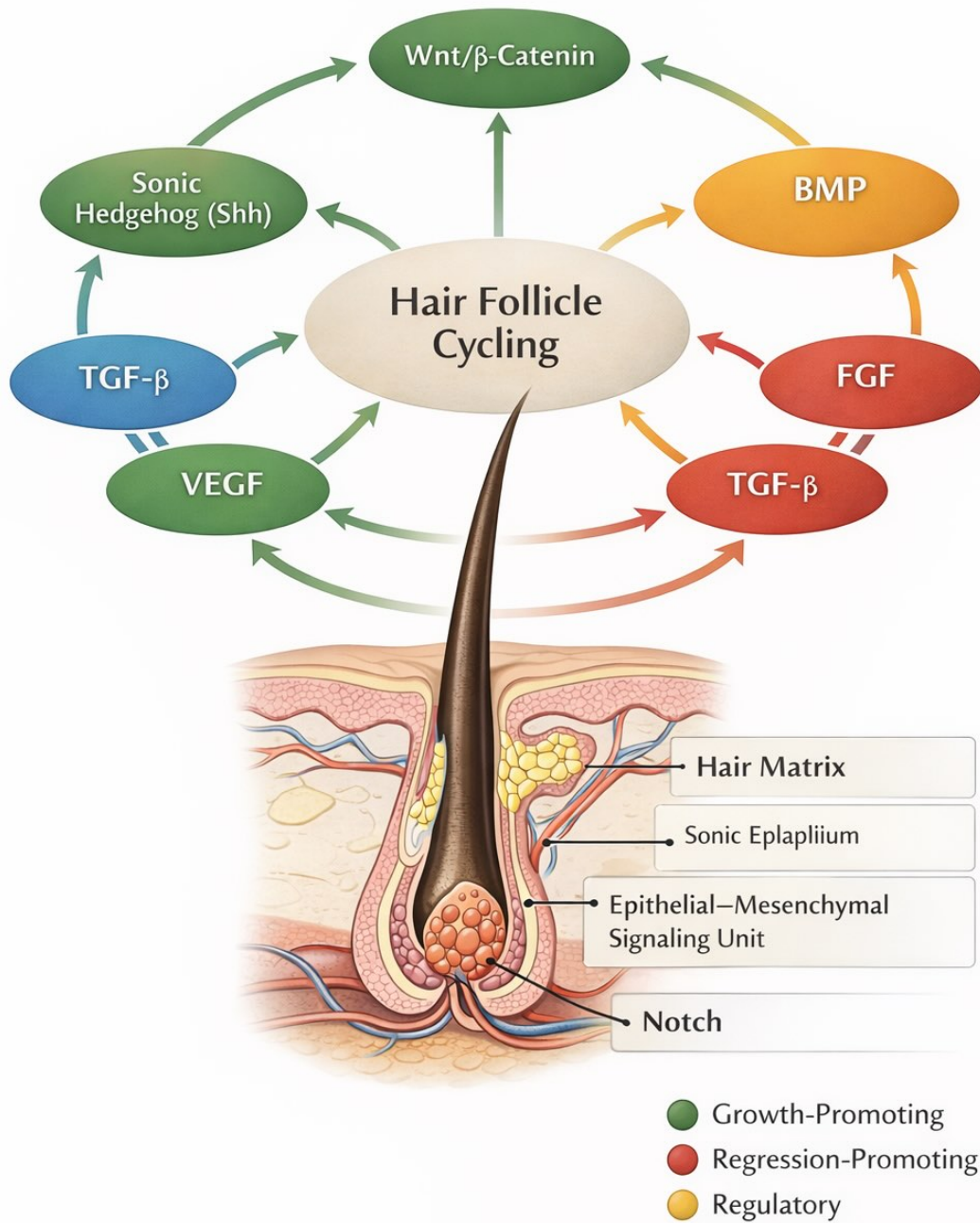


Figure 2: Integrated signaling pathways in hair follicle cycling

Wnt/ β -catenin signaling

Wnt signaling is central to anagen induction, playing a critical role in promoting the proliferation and differentiation of hair follicle stem cells (Rompolas & Greco, 2013). The β -catenin/Wnt signaling pathway, specifically within the dermal papilla, is indispensable for sustaining anagen hair growth and initiating new hair development in the initial postnatal hair cycle (Woo et al., 2012). Binding of the Wnt ligand to its frizzled receptor initiates a cascade that stabilizes β -catenin, allowing its translocation to the nucleus where it complexes with T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) transcription factor to activate Wnt target genes crucial for cell proliferation and differentiation (Sennett & Rendl, 2012). This pivotal pathway not only governs the initial hair germ activation but also orchestrates the subsequent proliferation and differentiation of epithelial lineages that form the new hair shaft (Lee & Choi, 2024).

Critical Wnt ligands in human hair follicle development are categorized by their specific roles in initiation and maturation: Wnt3, Wnt4, and Wnt6 as primary ligands for the earliest stage of HF induction, particularly hair placode formation, and secondary ligands such as Wnt10a and Wnt10b driving subsequent morphogenesis and follicular maturation (Lin et al., 2022). Wnt3, Wnt4, and Wnt10b, along with activation of downstream targets AXIN2 and LEF1 during the telogen-to-anagen transition and downregulation of the Wnt antagonist SFRP1, further facilitate stem cell activation and follicular regeneration (Hawkshaw et al., 2018; Hu et al., 2021).

Dihydrotestosterone, the principal active androgen generated via 5α -reductase, promotes hair follicle miniaturization in androgenetic alopecia through upregulation of DKK1 in dermal papilla cells, whose antagonism of Wnt/ β -catenin signaling suppresses stem cell differentiation and anagen progression (Dincheva et al., 2023; Joshi et al., 2020; Leirós et al., 2016).

Sonic hedgehog (Shh) signaling

The Sonic hedgehog signaling pathway is essential for orchestrating follicular morphogenesis, promoting matrix cell proliferation, and maintaining dermal papilla identity through regulatory loops such as Noggin–Shh interactions (Bellani et al., 2025; Woo et al., 2012). It functions synergistically with Wnt/ β -catenin pathways to drive epithelial proliferation, structural maturation of the follicle, and anagen maintenance during the proliferative surge (Bellani et al., 2025; Dincheva et al., 2023; Hu et al., 2021).

Bone morphogenetic protein (BMP) signaling

BMP signaling maintains stem cell quiescence during telogen via inhibitory ligands secreted from the dermal papilla and bulge region, counterbalanced by Wnt activation to regulate the hair cycle (Driskell et al., 2011; Rompolas & Greco, 2013; Sennett & Rendl, 2012). Thus, suppression of BMP, primarily through antagonists like Noggin secreted by dermal papilla

cells, is essential for anagen initiation and secondary hair germ formation, enabling the transition from a BMP-dominated quiescent state to proliferative Wnt/ β -catenin dominance (Bellani et al., 2025; Colin-Pierre et al., 2022). In androgenetic alopecia, aberrant BMP upregulation prolongs quiescence and impairs stem cell reactivation (Bellani et al., 2025). The expression levels of BMP-2 and BMP-4 undergo periodic changes throughout the hair follicle cycle, indicating their dynamic involvement in regulating follicular transitions (Liu et al., 2023). BMP proteins (ligand) binding with their BMPRa1 and BMPR2 receptors initiate a signaling cascade that ultimately regulates cell fate decisions, proliferation, and differentiation within the hair follicle (Lee & Tumber, 2012; Lin et al., 2022). And their interaction with the TGF- β family, playing a crucial role in development, homeostasis, and repair of tissues (Wang et al., 2022). This intricate interplay between BMP and TGF- β signaling cascades within the hair follicle microenvironment contributes significantly to regulating the delicate balance between proliferation, differentiation, and quiescence during the hair cycle (see TFG-beta below).

Notch signaling

Notch signaling plays a crucial role in hair follicle growth, serving as a master regulator of stem cell differentiation, hair shaft development, and inner root sheath formation (Wang et al., 2022; Zhang et al., 2024). By directing cell fate decisions, it prevents stem cells from adopting an epidermal identity and instead promotes their differentiation into hair shaft lineages (Wang et al., 2022; Zhang et al., 2013). Specifically, Notch1–3 receptors are essential for postnatal hair growth and structural follicle development (Rompolas & Greco, 2013). Furthermore, Notch signaling, influenced by both intrinsic oscillatory gene networks within hair follicle stem cells and extrinsic cues from the mesenchymal niche, modulates the periodicity of the hair cycle by interacting with FGF and Wnt pathways (Daszczuk et al., 2020; Harshuk-Shabso et al., 2020). This intricate interaction highlights a sophisticated regulatory mechanism where Notch signaling coordinates with other pathways to ensure the precise timing and execution of hair follicle regeneration (Daszczuk et al., 2020). The dynamic interplay between Notch signaling and other crucial pathways, such as BMP and Wnt, is fundamental for regulating stem cell activity during hair regeneration (Ji et al., 2021; Lee & Choi, 2024; Plikus et al., 2008).

Noggin signaling

Noggin, a potent BMP antagonist secreted by dermal papilla cells, is indispensable for anagen initiation by counteracting BMP-mediated quiescence of bulge stem cells during telogen (Botchkarev et al., 2001; Colin-Pierre et al., 2022). By neutralizing inhibitory BMP4 signaling, Noggin facilitates the telogen-to-anagen transition, upregulating Sonic hedgehog and Lef-1 to promote secondary hair germ formation, epithelial proliferation, and hair matrix regeneration (Botchkarev et al., 2001; Woo et al., 2012). Noggin and SHH have a synergistic relationship, with Noggin inducing SHH expression, further promoting cell proliferation and

hair follicle growth (Kulesa, 2000; Mullen & Wrana, 2017; Sharov et al., 2006; Wang et al., 2022).

Transforming Growth Factor-beta (TGF- β) Signaling

TGF- β signaling plays a complex, context-dependent role in hair follicle biology, generally promoting catagen entry and inhibiting anagen progression by inducing apoptosis and cell cycle arrest in epithelial cells (Chen et al., 2020). For instance, TGF- β 1 is highly expressed in the outer root sheath during late anagen and is implicated in facilitating the transition to catagen (Lee & Tumbar, 2012). Conversely, during the anagen phase, specific TGF- β family members, such as TGF- β 2, are secreted by the dermal papilla, contributing to the activation of the hair germ and stimulating anagen re-entry (Chen et al., 2015). This duality underscores the intricate regulatory balance of TGF- β , wherein its pro-apoptotic and proliferative roles are precisely timed to govern distinct phases of the hair cycle (Schneider et al., 2009). The interplay between TGF- β and other signaling pathways, such as Wnt/ β -catenin and BMP, is crucial for maintaining the precise timing of hair follicle cycling (Lin et al., 2022).

Fibroblast growth factor signaling

Fibroblast growth factor (FGF) signaling exerts diverse effects on hair follicle cycling. FGF7 and FGF10, secreted by dermal papilla cells, promote anagen initiation by stimulating epithelial stem cell proliferation and hair germ outgrowth (Colin-Pierre et al., 2022; Woo et al., 2012). Conversely, FGF5 drives anagen termination and catagen induction, thereby limiting hair length and regulating cycle duration (Driskell et al., 2011). FGF18 further modulates growth by suppressing anagen progression (Sennett & Rendl, 2012).

Vascular and metabolic signaling

Vascular endothelial growth factor-1 (VEGF-1) and insulin-like growth factor 1 (IGF-1) signaling promote hair follicle growth by enhancing angiogenesis, stimulating cellular proliferation in the hair matrix, and providing metabolic support to the dermal papilla, with reduced levels observed in androgenetic alopecia contributing to premature anagen termination (Patel, 2017; Trüeb, 2021).

Collectively, these pathways constitute a tightly regulated network that governs follicular activation, growth, differentiation, and regression. The spatial and temporal integration of these signals, often involving synergistic interactions like the balance between BMP6 and Wnt10b, remains the foundational mechanism dictating hair follicle cyclic homeostasis (Ji et al., 2021). Ongoing research aims to translate these molecular insights into clinical strategies that modulate these micro-environmental factors to reverse hair follicle miniaturization (Vasserot et al., 2019).

3. Molecular Drivers of Follicular Regression and Hair Loss

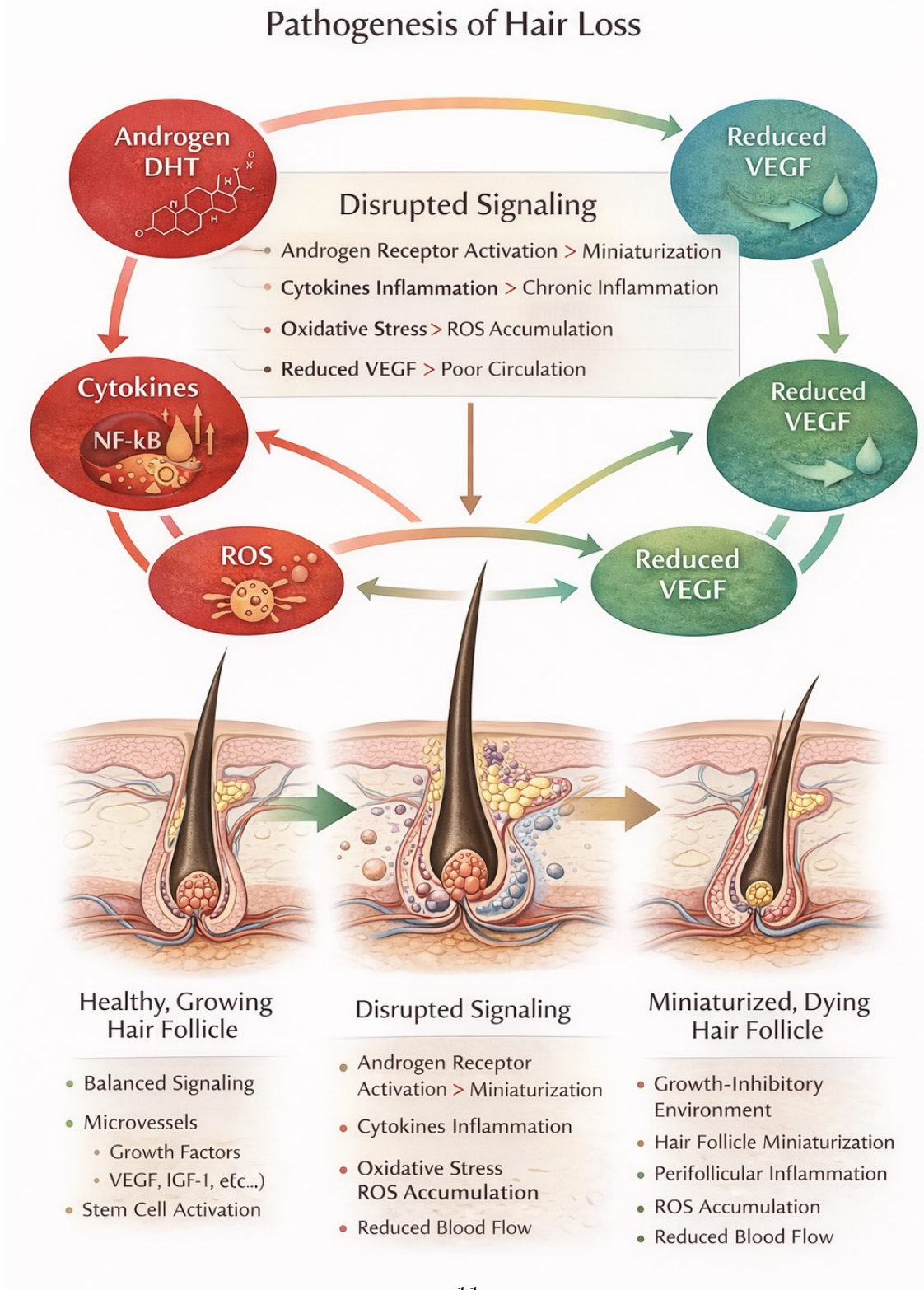


Figure 3: Pathogenesis of hair loss breakdown

While the hair follicle possesses intrinsic regenerative capacity, its stability is highly sensitive to perturbations in its signaling environment. Hair loss can therefore be understood as the cumulative result of converging molecular disruptions rather than a single dominant defect.

3.1 Androgen-Mediated Miniaturization

Androgen signaling plays a pivotal role in the pathogenesis of androgenetic alopecia (Leirós et al., 2016; Yue et al., 2022). Dihydrotestosterone (DHT), the primary active androgen produced via 5α -reductase, binds to androgen receptors in dermal papilla cells, reprogramming transcriptional networks that govern follicular size and hair cycle dynamics (Leirós et al., 2016; Yue et al., 2022). Over time, these alterations culminate in progressive miniaturization, shortened anagen duration, and conversion of terminal hairs to vellus-like structures (Dincheva et al., 2023; Leirós et al., 2016; Trüeb, 2021). Specifically, androgen receptor activation induces TGF- β 1 and TGF- β 2 expression from dermal papilla cells, inhibiting follicular angiogenesis while promoting catagen via apoptosis in epithelial cells (Trüeb, 2021; Yue et al., 2022). Additionally, androgens upregulate DKK1—a potent Wnt/ β -catenin antagonist—in dermal papilla cells, thereby suppressing proliferative signals critical for anagen maintenance and bulge stem cell differentiation (Leirós et al., 2016; Yue et al., 2022).

3.2 Chronic Microinflammation and Immune Signaling

A growing body of evidence supports a role for chronic, low-grade perifollicular inflammation in multiple forms of alopecia. Pro-inflammatory cytokines such as interleukin-1, interleukin-6, and TGF- β and NF- κ B signaling and promote premature catagen entry. These pro-inflammatory mediators alter the follicular microenvironment by impairing the recruitment of regulatory T cells, which are essential for maintaining the quiescence-to-activation equilibrium required for robust cycling (Wang et al., 2025; Wu et al., 2019). This inflammatory microenvironment disrupts epithelial–mesenchymal communication and can impair stem cell activation, contributing to persistent follicular dysfunction.

3.3 Oxidative Stress and Cellular Senescence

The follicular environment is metabolically active and therefore prone to generate reactive oxygen species (ROS). Accumulation of these ROS contributes to lipid peroxidation, DNA damage, and mitochondrial dysfunction, processes that impair cellular viability and stem cell function. Such oxidative stress can also amplify inflammatory signaling, creating feed-forward dynamics that accelerate follicular regression. Specifically, androgen-induced mitochondrial ROS accumulation in dermal papilla cells promotes the formation of mitochondria-associated endoplasmic reticulum membranes, triggering calcium-dependent cellular aging

(Liang et al., 2023). This mechanism further suppresses the expression of insulin-like growth factor 1, which is critical for maintaining anagen, thereby reinforcing the premature catagen transition (Trüeb, 2021).

3.4 Prostaglandin Imbalance

Prostaglandins act as key lipid mediators in follicular signaling, with imbalances—particularly elevated prostaglandin D2 levels—strongly implicated in hair cycle dysregulation and androgenetic alopecia pathogenesis (Patel, 2017; Yue et al., 2022). PGD2 contributes to follicular miniaturization by inhibiting hair growth and promoting premature catagen induction, often in synergy with androgen signaling, as testosterone production has been linked to PGD accumulation (Liang et al., 2023). These effects disrupt anagen maintenance and exacerbate inflammatory–metabolic perturbations within the follicular niche. In this context, prostaglandin signaling integrates into a broader inflammatory–metabolic axis, amplifying regression signals alongside oxidative stress and immune activation. Furthermore, the overexpression of prostaglandin D2 receptor 2 on dermal papilla cells underscores the susceptibility of these follicles to lipid-mediated signaling disruption, which consistently contributes to the progressive exhaustion of the follicular stem cell pool (Liang et al., 2023; Mao et al., 2023).

3.5 Microvascular and Metabolic Insufficiency

The dermal papilla relies on sufficient vascular supply for oxygen and nutrient delivery. Impaired VEGF signaling or microvascular compromise diminishes metabolic support to the follicle, thereby weakening its capacity to sustain anagen (Colin-Pierre et al., 2021; Yoon et al., 2019). From a systems perspective, vascular health serves as a permissive layer enabling other growth-promoting signals to translate into sustained follicular output. Consequently, local ischemia and reduced oxygenation heighten the dermal papilla’s sensitivity to androgenic and oxidative stress, reinforcing a self-perpetuating cycle of follicular regression (Marques et al., 2024). Beyond vascular insufficiency, recent research suggests that metabolic dysregulation—including disruption to the electron transport chain and redox imbalances—further impairs the energy-intensive process of follicle cycling (Sadgrove et al., 2023).

Taken together, these interconnected drivers—androgenic dysregulation, chronic microinflammation, oxidative stress, prostaglandin imbalance, and microvascular/metabolic insufficiency—collectively illustrate that hair loss reflects a systems-level disruption in follicular homeostasis. This multifactorial framework provides a mechanistic rationale for multi-target modulation across the perturbed signaling network. Future therapeutic strategies must therefore prioritize restoring this delicate equilibrium by simultaneously antagonizing androgenic signaling, mitigating inflammatory and oxidative triggers, correcting prostaglandin dysregula-

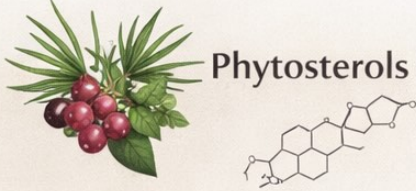

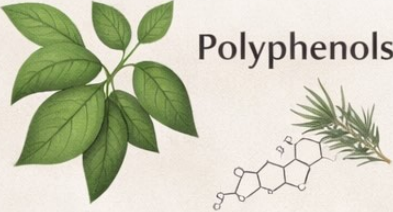



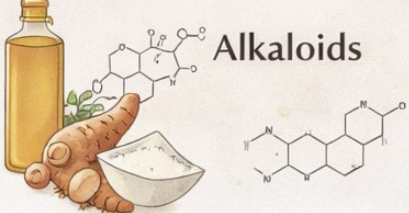

tion, and bolstering microvascular and metabolic support within the follicular niche (Patel, 2017; Sadgrove et al., 2023).

4. Phytochemical Classes and Molecular Targets

Plant-derived compounds encompass a broad range of biochemical classes that interact with human cellular signaling pathways. These include polyphenols and flavonoids; terpenoids; phytosterols; alkaloids. For instance, polyphenols and flavonoids are widely recognized for their capacity to neutralize oxidative stress through direct free radical scavenging and by upregulating endogenous antioxidant enzymes. Beyond their antioxidant properties, certain polyphenols, such as p-coumaric acid, also exhibit anti-inflammatory effects (Serruya & Maor, 2021). Terpenoids modulate vascular tone and enhance VEGF signaling to bolster microvascular perfusion (Marques et al., 2024) (Prugsakij et al., 2023), and phytosterols have demonstrated efficacy in modulating hormonal pathways relevant to androgenetic alopecia (Feldman et al., 2022). Alkaloids target enzymatic pathways to disrupt prostaglandin imbalances and metabolic dysregulation (Liang et al., 2023). This broad spectrum of bioactivity suggests that phytochemicals may offer a multifaceted approach to treating hair loss by addressing several underlying pathologies simultaneously (Park & Lee, 2021; Serruya & Maor, 2021).

5. Molecular Mechanisms of Botanical Modulation

Botanical Compounds Mapped to Molecular Targets

| Botanical Class | Targets |
|--|--|
|  <p>Phytosterols</p> |  <ul style="list-style-type: none"> 5α-Reductase Androgen Receptor |
|  <p>Polyphenols</p> |  <ul style="list-style-type: none"> NF-κB Cytokines Inflammation Reactive Oxygen Species |
|  <p>Terpenoids</p> |  <ul style="list-style-type: none"> VEGF Microcirculation 5α-Reductase |
|  <p>Alkaloids</p> |  <ul style="list-style-type: none"> Metabolic Enzymes PDE Inhibitors |

Botanical compounds exert their effects through multi-target interactions across the follicular signaling network, aligning with the distributed nature of hair cycle regulation. Phytosterols, structurally akin to cholesterol, inhibit 5α -reductase activity and modulate androgen receptor signaling, counteracting DHT-induced follicular miniaturization and TGF- β upregulation (Yue et al., 2022). Polyphenolic and flavonoid compounds deliver potent antioxidant and anti-inflammatory actions by scavenging reactive oxygen species, preserving mitochondrial function in dermal papilla cells, and suppressing NF- κ B activation along with pro-inflammatory cytokines such as IL-1, IL-6, and TNF (Liang et al., 2023; Patel, 2017). Terpenoids and flavonoids further activate pro-anagenic pathways, notably Wnt/ β -catenin signaling, while promoting anagen induction and maintenance via growth factor dynamics (He et al., 2026). Concurrently, terpenoids enhance microvascular perfusion through VEGF signaling and vascular tone modulation (Marques et al., 2024), whereas alkaloids disrupt prostaglandin D2 imbalances and associated metabolic dysregulation (Liang et al., 2023; Patel, 2017). Antioxidant phytochemicals mitigate oxidative stress, supporting electron transport chain integrity and redox homeostasis essential for energy-demanding follicular cycling (Sadgrove et al., 2023).

Taken together, these mechanisms underscore that botanical modulation is best understood as distributed regulation across androgenic, inflammatory, oxidative, vascular, and growth-associated domains, rather than single-pathway interventions (Feldman et al., 2022; Peng et al., 2021).

6. Network Pharmacology and Polybotanical Synergy

The complexity of hair follicle biology—encompassing distributed signaling across androgenic, inflammatory, oxidative, prostaglandin, microvascular, and metabolic domains—suggests that single-target interventions are inherently constrained by compensatory mechanisms and pathway redundancy (Sadgrove et al., 2023). Network pharmacology offers a robust framework for dissecting polybotanical interventions that concurrently engage multiple nodes within this interconnected signaling network (Mustafa et al., 2025). Polybotanical systems harness diverse phytochemical classes—including phytosterols, polyphenols, flavonoids, terpenoids, and alkaloids—to enable simultaneous modulation of androgen signaling (e.g., via 5α -reductase inhibition and AR antagonism), inflammatory cascades (e.g., NF- κ B suppression), oxidative stress pathways (e.g., ROS scavenging and mitochondrial preservation), prostaglandin imbalances, and growth factor dynamics (e.g., Wnt/ β -catenin activation and VEGF enhancement) (He et al., 2026; Liang et al., 2023; Marques et al., 2024; Patel, 2017; Yue et al., 2022). This synergistic interaction enables a more comprehensive restoration of the hair follicle microenvironment by addressing both the upstream hormonal triggers of miniaturization and the downstream failure of anagen-related signaling cascades (Serruya & Maor, 2021). By leveraging these multi-target synergies, network pharmacology strategies

facilitate the identification of novel therapeutic candidates that outperform conventional monotherapies by mitigating the limitations of pharmacological redundancy (Fang et al., 2024; Zhang et al., 2022).

7. Systems Biology Model of Follicular Regeneration

Hair follicle regeneration can be conceptualized as an emergent property of interacting signaling networks that include stem cell activation, immune signaling, metabolic regulation, and vascular support (Zhang et al., 2022). Perturbations in any one domain can propagate through the network and alter follicular fate, particularly when disruptions co-occur.

Botanical compounds, by interacting with multiple components of this network, may stabilize system dynamics and promote sustained anagen maintenance. Systems biology approaches—including transcriptomics, proteomics, and metabolomics—offer tools to map these interactions, identify pathway-sensitive biomarkers, and characterize response signatures associated with phytochemical exposure. Such methods may help define mechanistically coherent botanical combinations and clarify whether observed effects are driven by stem cell activation, dermal papilla reprogramming, microenvironmental stabilization, or integrated multi-compartment shifts.

8. Future Directions

Future research should integrate molecular and systems-level methodologies to refine our understanding of botanical modulation in follicular biology. Transcriptomic profiling of dermal papilla and epithelial stem cell populations exposed to phytochemicals may reveal gene-expression signatures associated with anagen induction, inflammatory suppression, or oxidative stress resilience. High-throughput screening of botanical libraries may identify candidate modulators of Wnt, Shh, BMP, and inflammatory pathways, enabling more precise mapping of phytochemical–pathway relationships.

In parallel, investigating scalp microbiome interactions with phytochemicals represents an emerging frontier, particularly since microbial metabolites can influence inflammatory tone and barrier function. Advances in delivery science may enhance the bioavailability of plant-derived molecules within follicular compartments, thereby improving the translation of molecular activity into sustained physiological effects. Finally, establishing standardized clinical protocols that correlate these high-throughput laboratory findings with long-term scalp phenotype changes will be essential for validating the therapeutic efficacy of these botanical interventions in diverse clinical populations (Park & Lee, 2021). Such longitudinal studies will be critical to addressing current gaps in clinical evidence regarding the variable efficacy

and slow onset of results often observed with these treatments(Hayes et al., 2007; Laurenceau et al., 2007).

9. Conclusion

Hair follicle cycling is governed by a complex network of interconnected molecular pathways, including Wnt, Shh, BMP, FGF, androgen, inflammatory, oxidative, and vascular signaling . Botanical compounds, with their diverse phytochemical profiles, can simultaneously modulate multiple components of this network(Park & Lee, 2021). A network pharmacology framework elucidates how polybotanical systems influence follicular regeneration in ways that align with the inherent complexity of hair follicle biology(Zhang et al., 2022). Continued molecular and systems-level investigations of plant-derived compounds could expand therapeutic strategies for hair growth disorders while supporting integrative approaches to long-term follicular health. Furthermore, as evidence of their multi-faceted clinical efficacy continues to emerge, these interventions may offer a reliable alternative or adjunct to conventional pharmacological treatments for various forms of alopecia (Choi et al., 2024). However, researchers must prioritize the development of rigorous, standardized clinical trials to overcome current limitations regarding the inconsistent availability of robust empirical evidence (Liu et al., 2023).

About the Author

Charit Seneviratne, PhD is a biomedical scientist and Director of Research at the AlviArmani Research Institute, where he has contributed to hair follicle and scalp research since 2007. Over the course of his tenure, Dr. Seneviratne has participated in translational research initiatives spanning experimental replication, protocol optimization in hair restoration workflows, and investigations into microscalp physiology. He has also contributed to the TR series and Ampligraf research programs, with a scientific focus on follicular signaling networks, oxidative stress biology, and systems-level approaches to tissue regeneration. His work integrates cellular signaling, phytochemistry, and network pharmacology to investigate biologically coherent strategies for follicular longevity and regeneration.

References

Alves, R. (2017). Androgenetic Alopecia: a Review and Emerging Treatments [Review of Androgenetic Alopecia: a Review and Emerging Treatments]. *Journal of Clinical Research in Dermatology*, 4(4), 1. Symbiosis Group. <https://doi.org/10.15226/2378-1726/4/4/00164>

Bellani, D., Patil, R., Prabhugate, A., Shahare, R., Gold, M. H., Kapoor, R., & Shome, D. (2025). Pathophysiological mechanisms of hair follicle regeneration and potential therapeutic strategies. *Stem Cell Research & Therapy*, *16*(1), 302. <https://doi.org/10.1186/s13287-025-04420-4>

Blanpain, C., & Fuchs, E. (2009). Epidermal homeostasis: a balancing act of stem cells in the skin [Review of Epidermal homeostasis: a balancing act of stem cells in the skin]. *Nature Reviews Molecular Cell Biology*, *10*(3), 207. Nature Portfolio. <https://doi.org/10.1038/nrm2636>

Botchkarev, V. A., Botchkareva, N. V., Nakamura, M., Huber, O., Funa, K., Lauster, R., Paus, R., & Gilchrist, B. A. (2001). Noggin is required for induction of the hair follicle growth phase in postnatal skin. *The FASEB Journal*, *15*(12), 2205. <https://doi.org/10.1096/fj.01-0207com>

Chen, C.-C., Plikus, M. V., Tang, P., Widelitz, R. B., & Chuong, C. (2015). The Modulatable Stem Cell Niche: Tissue Interactions during Hair and Feather Follicle Regeneration [Review of The Modulatable Stem Cell Niche: Tissue Interactions during Hair and Feather Follicle Regeneration]. *Journal of Molecular Biology*, *428*(7), 1423. Elsevier BV. <https://doi.org/10.1016/j.jmb.2015.07.009>

Chen, C.-L., Huang, W., Wang, E. H. C., Tai, K., & Lin, S. (2020). Functional complexity of hair follicle stem cell niche and therapeutic targeting of niche dysfunction for hair regeneration [Review of Functional complexity of hair follicle stem cell niche and therapeutic targeting of niche dysfunction for hair regeneration]. *Journal of Biomedical Science*, *27*(1). BioMed Central. <https://doi.org/10.1186/s12929-020-0624-8>

Choi, J. Y., Boo, M. Y., & Boo, Y. C. (2024). Can Plant Extracts Help Prevent Hair Loss or Promote Hair Growth? A Review Comparing Their Therapeutic Efficacies, Phytochemical Components, and Modulatory Targets. *Molecules*, *29*(10), 2288. <https://doi.org/10.3390/molecules29102288>

Chueh, S.-C., Lin, S., Chen, C.-C., Lei, M., Wang, L. M., Widelitz, R. B., Hughes, M. W., Jiang, T.-X., & Chuong, C. (2013). Therapeutic strategy for hair regeneration: hair cycle activation, niche environment modulation, wound-induced follicle neogenesis, and stem cell engineering [Review of Therapeutic strategy for hair regeneration: hair cycle activation, niche environment modulation, wound-induced follicle neogenesis, and stem cell engineering]. *Expert Opinion on Biological Therapy*, *13*(3), 377. Taylor & Francis. <https://doi.org/10.1517/14712598.2013.777777>

Colin-Pierre, C., Baraka, O. E., Danoux, L., Bardey, V., André, V., Ramont, L., & Brézillon, S. (2022). Regulation of stem cell fate by HSPGs: implication in hair follicle cycling [Review of Regulation of stem cell fate by HSPGs: implication in hair follicle cycling]. *Npj Regenerative Medicine*, *7*(1). Nature Portfolio. <https://doi.org/10.1038/s41536-022-00267-y>

Colin-Pierre, C., Berthélémy, N., Belloy, N., Danoux, L., Bardey, V., Rivet, R., Mine, S., Jeanmaire, C., Maquart, F., Ramont, L., & Brézillon, S. (2021). The Glypican-1/HGF/C-

Met and Glypican-1/VEGF/VEGFR2 Ternary Complexes Regulate Hair Follicle Angiogenesis. *Frontiers in Cell and Developmental Biology*, 9. <https://doi.org/10.3389/fcell.2021.781172>

Cotsarelis, G. (2005, December 8). Gene expression profiling gets to the root of human hair follicle stem cells. In *Journal of Clinical Investigation* (Vol. 116, Issue 1, p. 19). American Society for Clinical Investigation. <https://doi.org/10.1172/jci27490>

Daszczuk, P., Mazurek, P., Pieczonka, T. D., Olczak, A., Boryń, Ł. M., & Kobiela, K. (2020). An Intrinsic Oscillation of Gene Networks Inside Hair Follicle Stem Cells: An Additional Layer That Can Modulate Hair Stem Cell Activities [Review of An Intrinsic Oscillation of Gene Networks Inside Hair Follicle Stem Cells: An Additional Layer That Can Modulate Hair Stem Cell Activities]. *Frontiers in Cell and Developmental Biology*, 8. Frontiers Media. <https://doi.org/10.3389/fcell.2020.595178>

Dincheva, I., Badjakov, I., & Galunska, B. (2023). New Insights in the Research of Bioactive Compounds from Plant Origin with Nutraceutical and Pharmaceutical Potential. In MDPI eBooks. <https://doi.org/10.3390/books978-3-0365-6509-5>

Driskell, R. R., Clavel, C., Rendl, M., & Watt, F. M. (2011). Hair follicle dermal papilla cells at a glance. *Journal of Cell Science*, 124(8), 1179. <https://doi.org/10.1242/jcs.082446>

Duverger, O., & Morasso, M. I. (2013). To grow or not to grow: Hair morphogenesis and human genetic hair disorders [Review of To grow or not to grow: Hair morphogenesis and human genetic hair disorders]. *Seminars in Cell and Developmental Biology*, 22. Elsevier BV. <https://doi.org/10.1016/j.semedb.2013.12.006>

Fan, X., Chen, J., Zhang, Y., Wang, S., Zhong, W., Yuan, H., Wu, X., Wang, C., Zheng, Y., Wei, Y., & Xiao, Y. (2022). Alpinetin promotes hair regeneration via activating hair follicle stem cells. *Chinese Medicine*, 17(1). <https://doi.org/10.1186/s13020-022-00619-2>

Fang, C., Yang, H., Dai, Z., Fan, D., & Deng, J. (2024). Natural bioactive compounds as potential sources for alleviation and treatment of androgenetic alopecia: A research advance. *eFood*, 5(2). <https://doi.org/10.1002/efd2.138>

Feldman, P. R., Feldman, O. J., Guevara-Aguirre, J., & Fiebig, K. M. (2022). Sex differences in clinical trials of ALRV5XR treatment of androgenetic alopecia and telogen effluvium. *Frontiers in Medicine*, 9. <https://doi.org/10.3389/fmed.2022.918058>

Harshuk-Shabso, S., Dressler, H., Niehrs, C., Aamar, E., & Enshell-Seijffers, D. (2020). Fgf and Wnt signaling interaction in the mesenchymal niche regulates the murine hair cycle clock. *Nature Communications*, 11(1), 5114. <https://doi.org/10.1038/s41467-020-18643-x>

Hawkshaw, N. J., Hardman, J., Haslam, I. S., Shahmalak, A., Gilhar, A., Lim, X., & Paus, R. (2018). Identifying novel strategies for treating human hair loss disorders: Cyclosporine A suppresses the Wnt inhibitor, SFRP1, in the dermal papilla of human scalp hair follicles.

PLoS Biology, 16(5). <https://doi.org/10.1371/journal.pbio.2003705>

Hayes, A. M., Laurenceau, J., Feldman, G., Strauss, J. L., & Cardaciotto, L. (2007). Change is not always linear: The study of nonlinear and discontinuous patterns of change in psychotherapy [Review of Change is not always linear: The study of nonlinear and discontinuous patterns of change in psychotherapy]. *Clinical Psychology Review*, 27(6), 715. Elsevier BV. <https://doi.org/10.1016/j.cpr.2007.01.008>

He, B., Weng, Y., Luo, P., Xu, Z., Yan, H., Yang, B., He, Q., Lu, J., & Yang, X. (2026). Exploring the potential of natural products in treating alopecia areata. *Journal of Pharmaceutical Analysis*, 101539. <https://doi.org/10.1016/j.jpha.2025.101539>

Hu, X., Li, Z., Zhang, D.-Y., Yang, Y.-C., Fu, S., Zhang, Z.-Q., Yang, R., & Xiong, K. (2021). A systematic summary of survival and death signalling during the life of hair follicle stem cells [Review of A systematic summary of survival and death signalling during the life of hair follicle stem cells]. *Stem Cell Research & Therapy*, 12(1). BioMed Central. <https://doi.org/10.1186/s13287-021-02527-y>

Hughes, K., Ho, R., Chazaud, C., Hermitte, S., Greff, S., Butaud, J., Filaire, E., Ranouille, E., Berthon, J., & Raharivelomanana, P. (2021). In Vitro Hair Dermal Papilla Cells Induction by *Fagraea berteriana*, a Tree of the Marquesan Cosmetopoeia (French Polynesia). *Cosmetics*, 8(1), 13. <https://doi.org/10.3390/cosmetics8010013>

Ji, S., Zhu, Z., Sun, X., & Fu, X. (2021). Functional hair follicle regeneration: an updated review. *Signal Transduction and Targeted Therapy*, 6(1), 66. <https://doi.org/10.1038/s41392-020-00441-y>

Joshi, P. S., Patil, Y., Paul, T., & Apte, K. (2020). Phytotherapeutic Interventions using Rodent Models of Hair Loss: Current Research and Future Strategy. *Indian Journal of Pharmaceutical Sciences*, 82(5). <https://doi.org/10.36468/pharmaceutical-sciences.712>

Kulesa, H. (2000). Inhibition of Bmp signaling affects growth and differentiation in the anagen hair follicle. *The EMBO Journal*, 19(24), 6664. <https://doi.org/10.1093/emboj/19.24.6664>

Laurenceau, J., Hayes, A. M., & Feldman, G. (2007). Some methodological and statistical issues in the study of change processes in psychotherapy [Review of Some methodological and statistical issues in the study of change processes in psychotherapy]. *Clinical Psychology Review*, 27(6), 682. Elsevier BV. <https://doi.org/10.1016/j.cpr.2007.01.007>

Lee, J. H., & Choi, S. (2024). Deciphering the molecular mechanisms of stem cell dynamics in hair follicle regeneration. *Experimental & Molecular Medicine*, 56(1), 110. <https://doi.org/10.1038/s12276-023-01151-5>

Lee, J., & Tumbar, T. (2012). Hairy tale of signaling in hair follicle development and cycling [Review of Hairy tale of signaling in hair follicle development and cycling]. *Seminars in Cell*

and *Developmental Biology*, 23(8), 906. Elsevier BV. <https://doi.org/10.1016/j.semcdb.2012.08.003>

Leirós, G. J., Ceruti, J. M., Castellanos, M. L., Kusinsky, A. G., & Balañá, M. E. (2016). Androgens modify Wnt agonists/antagonists expression balance in dermal papilla cells preventing hair follicle stem cell differentiation in androgenetic alopecia. *Molecular and Cellular Endocrinology*, 439, 26. <https://doi.org/10.1016/j.mce.2016.10.018>

Liang, A., Fang, Y., Ye, L., Meng, J., Wang, X., Chen, J., & Xu, X. (2023). Signaling pathways in hair aging. *Frontiers in Cell and Developmental Biology*, 11, 1278278. <https://doi.org/10.3389/fcell.2023.1278278>

Lin, X., Liang, Z., & He, J. (2022). Morphogenesis, Growth Cycle and Molecular Regulation of Hair Follicles [Review of Morphogenesis, Growth Cycle and Molecular Regulation of Hair Follicles]. *Frontiers in Cell and Developmental Biology*, 10. Frontiers Media. <https://doi.org/10.3389/fcell.2022.899095>

Liu, D., Xu, Q., Meng, X., Liu, X., & Liu, J. (2023). Status of research on the development and regeneration of hair follicles. *International Journal of Medical Sciences*, 21(1), 80. <https://doi.org/10.7150/ijms.88508>

Mao, Y., Liu, P., Wei, J., Xie, Y., Zheng, Q., Li, R., & Yao, J. (2023). Cell Therapy for Androgenetic Alopecia: Elixir or Trick? [Review of Cell Therapy for Androgenetic Alopecia: Elixir or Trick?]. *Stem Cell Reviews and Reports*, 19(6), 1785. Springer Nature. <https://doi.org/10.1007/s12015-023-10532-2>

Marques, M. F., Simão, A. J. M., Bellizia, A. L., Oliveira, N. S. de, & Cruz-Silva, I. (2024). The efficacy of using platelet-rich plasma (PRP) in the treatment of androgenic alopecia: a literature review [Review of The efficacy of using platelet-rich plasma (PRP) in the treatment of androgenic alopecia: a literature review]. *Journal of Drug Delivery and Therapeutics*, 14(5), 185. Society of Pharmaceutical Technocrats. <https://doi.org/10.22270/jddt.v14i5.6598>

Mullen, A. C., & Wrana, J. L. (2017). TGF- β Family Signaling in Embryonic and Somatic Stem-Cell Renewal and Differentiation [Review of TGF- β Family Signaling in Embryonic and Somatic Stem-Cell Renewal and Differentiation]. *Cold Spring Harbor Perspectives in Biology*, 9(7). Cold Spring Harbor Laboratory Press. <https://doi.org/10.1101/cshperspect.a022186>

Mustafa, A. M., El-Shiekh, R. A., Faheem, S. A., Fawzy, M., Said, M. A., Mohamed, A. F., Hatem, S., & Mandour, A. A. (2025). Lupeol: an updated review utilizing AI-assisted predictive tools for enhanced therapeutic insights into lupeol's potential for alopecia management. *Future Journal of Pharmaceutical Sciences*, 11(1). <https://doi.org/10.1186/s43094-025-00878-4>

Ohyama, M. (2019). Use of human intra-tissue stem/progenitor cells and induced pluripotent stem cells for hair follicle regeneration [Review of Use of human intra-tissue stem/progenitor cells and induced pluripotent stem cells for hair follicle regeneration]. *Inflammation and*

Regeneration, 39(1). BioMed Central. <https://doi.org/10.1186/s41232-019-0093-1>

Park, S. (2022). Hair Follicle Morphogenesis During Embryogenesis, Neogenesis, and Organogenesis [Review of Hair Follicle Morphogenesis During Embryogenesis, Neogenesis, and Organogenesis]. *Frontiers in Cell and Developmental Biology*, 10. Frontiers Media. <https://doi.org/10.3389>

Park, S., & Lee, J. (2021). Modulation of Hair Growth Promoting Effect by Natural Products. *Pharmaceutics*, 13(12), 2163. <https://doi.org/10.3390/pharmaceutics13122163>

Patel, B. (2017). Addressing Androgenetic Alopecia-A Complex Disorder-with a Multilateral Treatment Strategy. *MOJ Bioequivalence & Bioavailability*, 3(1). <https://doi.org/10.15406/mojbb.2017.03>

Peng, Y., Peng, C., Wu, Y., Sun, C., & Li, X. (2021). Chemical profiles of the active fraction from *Prinsepia utilis* Royle leaves and its anti-benign prostatic hyperplasia evaluation in animal models. *BMC Complementary Medicine and Therapies*, 21(1). <https://doi.org/10.1186/s12906-021-03446-4>

Plikus, M. V., Mayer, J. A., Cruz, D. de la, Baker, R. E., Maini, P. K., Maxson, R., & Chuong, C. (2008). Cyclic dermal BMP signalling regulates stem cell activation during hair regeneration. *Nature*, 451(7176), 340. <https://doi.org/10.1038/nature06457>

Prugsakij, W., Numsawat, S., Netchareonsirisuk, P., Tengamnuay, P., & De-Eknamkul, W. (2023). Mechanistic synergy of hair growth promotion by the *Avicennia marina* extract and its active constituent (avicequinone C) in dermal papilla cells isolated from androgenic alopecia patients. *PLoS ONE*, 18(4). <https://doi.org/10.1371/journal.pone.0284853>

Rompolas, P., & Greco, V. (2013). Stem cell dynamics in the hair follicle niche [Review of Stem cell dynamics in the hair follicle niche]. *Seminars in Cell and Developmental Biology*, 34. Elsevier BV. <https://doi.org/10.1016/j.semcd.2013.12.005>

Sadgrove, N. J., Batra, S. K., Barreto, D. G., & Rapaport, J. A. (2023). An Updated Etiology of Hair Loss and the New Cosmeceutical Paradigm in Therapy: Clearing ‘the Big Eight Strikes.’ *Cosmetics*, 10(4), 106. <https://doi.org/10.3390/cosmetics10040106>

SANTOS, Z. X. S., Avci, P., & Hamblin, M. R. (2015). Drug discovery for alopecia: gone today, hair tomorrow [Review of Drug discovery for alopecia: gone today, hair tomorrow]. *Expert Opinion on Drug Discovery*, 10(3), 269. Taylor & Francis. <https://doi.org/10.1517/17460441.2015.1000>

Sarkar, F. H., Li, Y., Wang, Z., & Kong, D. (2009). Cellular signaling perturbation by natural products [Review of Cellular signaling perturbation by natural products]. *Cellular Signalling*, 21(11), 1541. Elsevier BV. <https://doi.org/10.1016/j.cellsig.2009.03.009>

Schneider, M. R., Schmidt-Ullrich, R., & Paus, R. (2009). The Hair Follicle as a Dynamic Miniorgan. *Current Biology*, 19(3). <https://doi.org/10.1016/j.cub.2008.12.005>

Sennett, R., & Rendl, M. (2012). Mesenchymal–epithelial interactions during hair follicle

morphogenesis and cycling [Review of Mesenchymal–epithelial interactions during hair follicle morphogenesis and cycling]. *Seminars in Cell and Developmental Biology*, 23(8), 917. Elsevier BV. <https://doi.org/10.1016/j.semcdb.2012.08.011>

Serruya, R., & Maor, Y. (2021). Hair growth-promotion effects at the cellular level and antioxidant activity of the plant-based extract Phyllotex™. *Heliyon*, 7(9). <https://doi.org/10.1016/j.heliyon.2021.09.001>

Sharov, A. A., Sharova, T., Mardaryev, A. N., Vignano, A. T. di, Atoyán, R., Weiner, L., Yang, S., Brissette, J. L., Dotto, G. P., & Botchkarev, V. A. (2006). Bone morphogenetic protein signaling regulates the size of hair follicles and modulates the expression of cell cycle-associated genes. *Proceedings of the National Academy of Sciences*, 103(48), 18166. <https://doi.org/10.1073/pnas.0608899103>

Soe, Z. C., Zin, Z., Visuttijai, K., & Chanvorachote, P. (2023). Potential Natural Products Regulation of Molecular Signaling Pathway in Dermal Papilla Stem Cells. *Molecules*, 28(14), 5517. <https://doi.org/10.3390/molecules28145517>

Trüeb, R. M. (2021). Understanding Pattern Hair Loss—Hair Biology Impacted by Genes, Androgens, Prostaglandins and Epigenetic Factors [Review of Understanding Pattern Hair Loss—Hair Biology Impacted by Genes, Androgens, Prostaglandins and Epigenetic Factors]. *Indian Journal of Plastic Surgery*, 54(4), 385. Thieme Medical Publishers (Germany). <https://doi.org/10.1055/s-0041-1739252>

Vasserot, A. P., Geyfman, M., & Poloso, N. J. (2019). Androgenetic alopecia: combing the hair follicle signaling pathways for new therapeutic targets and more effective treatment options. *Expert Opinion on Therapeutic Targets*, 23(9), 755. <https://doi.org/10.1080/14728222.2019.1659779>

Vatanashevanopakorn, C., & Sartyoungkul, T. (2023). iPSC-based approach for human hair follicle regeneration [Review of iPSC-based approach for human hair follicle regeneration]. *Frontiers in Cell and Developmental Biology*, 11. Frontiers Media. <https://doi.org/10.3389/fcell.2023.11490>

Wang, J., Wang, L., Gao, S., & Li, X. (2025). Recent Advances in the Role of Fibroblast Growth Factors in Hair Follicle Growth. *Biomolecules*, 15(8), 1198. <https://doi.org/10.3390/biom15081198>

Wang, X., Liu, Y., He, J., Wang, J., Chen, X., & Yang, R. (2022). Regulation of signaling pathways in hair follicle stem cells. *Burns & Trauma*, 10. <https://doi.org/10.1093/burnst/tkac022>

Woo, W., Zhen, H. H., & Oro, A. E. (2012). Shh maintains dermal papilla identity and hair morphogenesis via a Noggin–Shh regulatory loop. *Genes & Development*, 26(11), 1235. <https://doi.org/10.1101/gad.187401.112>

Wu, P., Zhang, Y., Xing, Y., Xu, W., Guo, H., Deng, F., Ma, X., & Li, Y. (2019). The balance of Bmp6 and Wnt10b regulates the telogen-anagen transition of hair follicles. *Cell Communication and Signaling*, 17(1). <https://doi.org/10.1186/s12964-019-0330-x>

- Wu, S., Kou, X., Niu, Y., Liu, Y., Zheng, B., Ma, J., Liu, M., & Xue, Z. (2023). Progress on the mechanism of natural products alleviating androgenetic alopecia. *European Journal of Medicinal Chemistry*, *264*, 116022. <https://doi.org/10.1016/j.ejmech.2023.116022>
- Yoon, S., Dieterich, L. C., Karaman, S., Proulx, S. T., Bachmann, S. B., Sciaroni, C., & Detmar, M. (2019). An important role of cutaneous lymphatic vessels in coordinating and promoting anagen hair follicle growth. *PLoS ONE*, *14*(7). <https://doi.org/10.1371/journal.pone.0220341>
- Yue, Z., Yang, F., Zhang, J., Li, J., & Chuong, C. (2022). Regulation and dysregulation of hair regeneration: aiming for clinical application [Review of Regulation and dysregulation of hair regeneration: aiming for clinical application]. *Cell Regeneration*, *11*(1). Springer Nature. <https://doi.org/10.1186/s13619-022-00122-x>
- Zhang, Y., Cui, J., Cang, Z.-Q., Pei, J., Zhang, X., Song, B., Fan, X., Ma, X., & Yang, L. (2024). Hair follicle stem cells promote epidermal regeneration under expanded condition. *Frontiers in Physiology*, *15*. <https://doi.org/10.3389/fphys.2024.1306011>
- Zhang, Y., Yü, J., Shi, C., Huang, Y., Wang, Y., Tian, Y., & Yang, J. (2013). Lef1 Contributes to the Differentiation of Bulge Stem Cells by Nuclear Translocation and Cross-Talk with the Notch Signaling Pathway. *International Journal of Medical Sciences*, *10*(6), 738. <https://doi.org/10.7150/ijms.5693>
- Zhang, Y., Zhang, S., Long, Y., Wang, W., Du, F., Li, J., Jin, F., & Li, Z. (2022). Stimulation of hair growth by Tianma Gouteng decoction: Identifying mechanisms based on chemical analysis, systems biology approach, and experimental evaluation. *Frontiers in Pharmacology*, *13*. <https://doi.org/10.3389/fphar.2022.1073392>