

# Traditional Chinese medicine approaches in treating alopecia: mechanisms, evidence, and future directions

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## Author contributions

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## Competing interests

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## Abbreviations

TCM, traditional Chinese medicine; AGA, androgenetic alopecia; AA, alopecia areata; JAK, Janus kinase; hDPCs, human dermal papilla cells; HFSCs, hair follicle stem cells; VEGF, vascular endothelial growth factor; TGF- $\beta$ , transforming growth factor- $\beta$ ; HF, hair follicle; DP, dermal papilla; FGF, fibroblast growth factor; IGF, insulin-like growth factor; DHT, dihydrotestosterone; AR, androgen receptor; ROS, reactive oxygen species.

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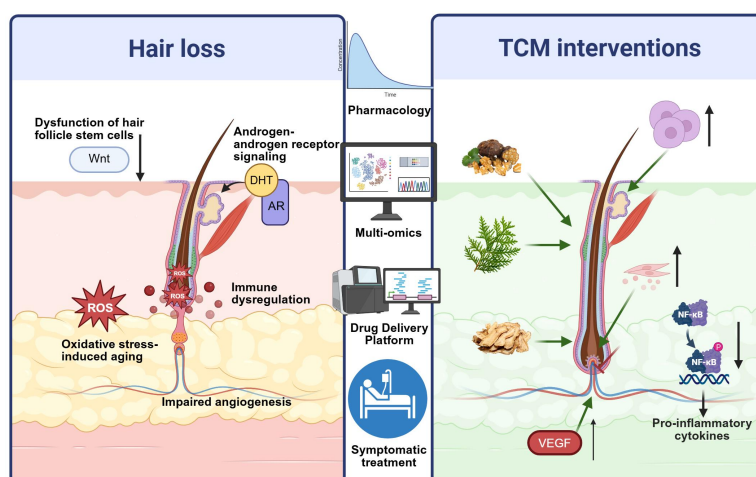
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## Abstract

Alopecia is a highly prevalent dermatological disorder characterized by dysregulation of hair follicle cycling, stem cell exhaustion, inflammatory activation, and hormonal imbalance. Currently approved pharmacotherapies provide limited efficacy and are often associated with adverse effects, highlighting an unmet need for multi-targeted and biologically integrative treatment strategies. Traditional Chinese Medicine (TCM), with its long-standing clinical use and multi-component, multi-target characteristics, has emerged as a promising complementary approach for hair loss management. In this review, we integrate hair follicle biology with classical TCM theory to elucidate the mechanistic basis of TCM interventions in alopecia. We summarize key molecules and cellular processes underlying hair loss, including hair follicle stem cell dysfunction, androgen-androgen receptor signaling, oxidative stress-induced aging, immune dysregulation, and impaired angiogenesis. Frequently prescribed TCM herbs and representative formulas, such as *Polygonum multiflorum*, *Platycladus orientalis*, *Angelica sinensis*, and Shi-Bi-Man, are discussed with respect to their bioactive constituents and experimental effects on dermal papilla cells, stem cell activation, inflammatory pathways, and follicular microcirculation. Although some pharmacological and preliminary clinical evidence support the therapeutic potential of TCM for treating alopecia, substantial challenges remain, including insufficient standardization of herbal preparations, limited mechanistic validation, and a lack of high-quality randomized controlled trials. Future integration of systems pharmacology, multi-omics technologies, and advanced drug-delivery platforms may facilitate the translation of TCM from empirical practice to evidence-based therapy for hair loss.

**Keywords:** alopecia; traditional Chinese medicine; herbs and formulas; hair regeneration; signaling pathway



**Highlights**

1. This review elucidates how Traditional Chinese Medicine (TCM) offers a holistic, multi-component, and multi-target therapeutic strategy for treating alopecia.
2. We establish links classical TCM syndromes (e.g., qi and blood deficiency) to molecular and cellular mechanisms (e.g., hair cycle, hormones, aging, immune dysregulation, and angiogenesis).
3. This review provides a scientific framework for understanding the therapeutic efficacy of TCM and identifies key bioactive compounds and their cellular targets.

**Medical history of objective**

In TCM, hair growth is considered closely related to the state of qi and blood, as well as the functional balance of the internal organs, especially the liver and kidneys. Classical TCM theory holds that hair is nourished by blood and rooted in kidney essence. Therefore, when qi and blood are sufficient and kidney essence is abundant, the hair is thought to be well nourished, appearing dark, lustrous, and vigorous. Conversely, deficiency of qi and blood or dysfunction of the internal organs may lead to poor hair nourishment, resulting in dry, brittle hair and eventual hair loss. From this perspective, alopecia is regarded not merely as a local disorder of the hair, but also as an external manifestation of an internal systemic imbalance. This concept is rooted in classical TCM literature, such as the *Huangdi Neijing Suwen*, compiled by Wang Bing of the Tang Dynasty (762.C.E.), which emphasizes the close relationship between hair condition, kidney essence, and the sufficiency of qi and blood.

**Introduction**

Alopecia, encompassing androgenetic alopecia (AGA), alopecia areata (AA), and various scarring and non-scarring forms, is a highly prevalent skin disorder that significantly impairs patients' quality of life and psychosocial well-being [1–3]. AGA is the predominant form of hair loss, accounting for ~70% of cases, followed by AA and other forms [4]. The associated psychosocial burden is considerable, with 30–40% of patients experiencing comorbid anxiety or depression [5]. Despite the multifactorial pathogenesis of hair loss, currently approved pharmacotherapies: minoxidil, finasteride, and Janus kinase (JAK) inhibitors, remain limited by modest efficacy, notable adverse effects, and the requirement for long-term administration. These limitations have spurred a sustained interest in alternative or complementary therapeutic strategies capable of simultaneously targeting multiple pathogenic pathways [6–10]. Consequently, the search for safe, multi-targeted, and biologically integrative therapies remains a critical priority in dermatological research.

In recent decades, Traditional Chinese medicine (TCM) has attracted growing global attention as an alternative and complementary approach to hair-loss management [11, 12]. TCM regards hair as the 'surplus of blood,' intrinsically linked to the health of the Liver and Kidney systems. Classical theory primarily attributes alopecia to Liver-Kidney deficiency (a depletion of foundational 'essence' and functional reserves that govern growth, regeneration, and hormonal balance) and Qi-Blood deficiency (an impairment of bioenergetic functional capacity and nutritional perfusion required for hair follicle maintenance) [13]. Various herbal medicines, such as *Platycladus orientalis* (Cebaiye), *Polygonum multiflorum* (Heshouwu), and *Cuscuta chinensis* (Tusizi), are believed to nourish the liver and kidney, invigorate blood circulation, and promote hair growth [14]. The bioactive compounds in these herbs, such as tetrahydroxystilbene glucoside (TSG) and  $\beta$ -sitosterol, have been shown to modulate several signaling pathways crucial for hair follicle regulation, including the Wnt/ $\beta$ -catenin pathway, PI3K/Akt pathway, and TGF- $\beta$  signaling [14, 15]. Collectively, these pathways play pivotal roles in

hair follicle development, the regulation of the hair cycle, and the pathogenesis of various forms of alopecia.

Hair loss, particularly AGA, is characterized by intricate molecular mechanisms that culminate in the shortening of the anagen phase of the hair cycle, diminished hair follicle size, and premature hair follicle regression. In recent years, research has identified numerous cellular and molecular factors in hair follicle biology, including dermal papilla cells (DPCs), hair follicle stem cells (HFSCs), and signaling molecules such as vascular endothelial growth factor (VEGF),  $\beta$ -catenin, and transforming growth factor- $\beta$  (TGF- $\beta$ ) [16]. Dysregulation of these pathways has been demonstrated to result in a reduction in follicular regeneration and hair growth, a characteristic feature of conditions such as AGA and AA.

Nevertheless, accumulating the mounting body of evidence that attests to the efficacy of TCM in the treatment of alopecia, the extant literature remains disorganized and fragmented. The majority of studies to date have focused on either single compounds or individual herbs. There is a paucity of research that connects hair follicle biology, alopecia pathophysiology, and TCM mechanisms. Moreover, the limitations in methodology inherent to clinical trials, such as small sample sizes and the absence of standardization in treatment protocols, are frequently observed.

This review aims to provide an integrated perspective on the role of TCM in the treatment of alopecia. It covers the underlying biological mechanisms of hair loss, the pathophysiology of alopecia, and the potential of TCM herbs and formulas to regulate key molecular pathways involved in hair follicle growth. Furthermore, the recent preclinical and clinical evidence will be discussed, as well as the challenges and future directions for TCM-based therapies in the field of alopecia treatment.

**Biology of the hair follicle and molecular pathways underlying alopecia****Overview of hair follicle structure and mechanism of hair loss**

The hair follicle (HF) is a dynamic mini-organ that undergoes continuous cycles of growth (anagen), regression (catagen), and rest (telogen) [17, 18]. During anagen, which lasts 2–8 years in humans, rapid proliferation of secondary hair germ cells and matrix cells occurs, driven by signals from the dermal papilla (DP) [19]. Catagen is a brief apoptosis-driven involution phase (2–3 weeks) during which the lower two-thirds of the HF regresses [20]. Finally, during telogen (approximately 3 months), the follicle remains dormant until specific activation signals trigger a new anagen phase [20]. Dysregulation of this cycle, specifically a shortened anagen or prolonged telogen, is the clinical hallmark of androgenetic alopecia and telogen effluvium [21]. Each cycle is tightly regulated by reciprocal interactions between epithelial and mesenchymal compartments. The DP serves as a key regulatory hub, secreting growth factors that activate quiescent HFSCs in the bulge region to re-enter the anagen phase and initiate new hair shaft formation [22]. Surrounding epithelial stem cells residing in the bulge and secondary hair germ also promote the formation of new hair follicles in response to dermal signals. Dysregulation of these cells is the biological foundation of alopecia [23].

**HFSCs and DPCs**

HFSCs reside in the bulge region, expressing markers such as CD34 and K15, and possess remarkable self-renewal and regenerative capacity. They remain quiescent during telogen and are activated during early anagen under the influence of DP-derived signals such as Wnt ligands, fibroblast growth factor (FGF) 7 and insulin-like growth factor 1 (IGF-1) [24–26]. DPCs function as the inductive core of the HF. They regulate epithelial–mesenchymal interactions through paracrine factors, including Wnts, BMP inhibitors and VEGF.

**Molecular signaling pathways in hair growth regulation**

Normal hair follicle cycling and regeneration require the coordinated regulation of multiple conserved signaling pathways. TCM has a long

history of treating hair loss, and its mechanism of action is characterized by multi-component and multi-target synergy. It can simultaneously intervene in multiple pathological processes of hair loss, reflecting the advantages of overall regulation and personalized treatment [27]. With the development of modern research technologies, the mechanisms of Chinese herbal medicine in treating hair loss have become increasingly clear [28]. This chapter will explain the mechanisms by which Chinese herbal medicine treats hair loss based on different pathological processes from five key perspectives: hair cycle, hormones, aging, immune inflammation, and angiogenesis, in order to provide scientific evidence for clinical application and drug development (Figure 1).

**Regulating the HF cycle and regeneration.** Hair loss is often closely related to abnormalities in the regulation of the HF cycle. As a complete regenerative system, the HF's growth cycle sequentially includes the anagen, catagen, and telogen [29]. In pathological conditions, the anagen phase is often shortened, and HFs prematurely enter the catagen phase, thereby resulting in reduced hair production and/or an increased telogen proportion, ultimately causing hair loss [30]. HF cycling and regeneration rely on the precise coordination of multiple conserved signaling pathways. Accordingly, regulating HF cycle transitions has become one of the key strategies for preventing and treating hair loss. Active ingredients in Chinese herbal medicine can directly influence the HF cycle process and regenerative capacity by modulating key signaling pathways such as Wnt/ $\beta$ -catenin.

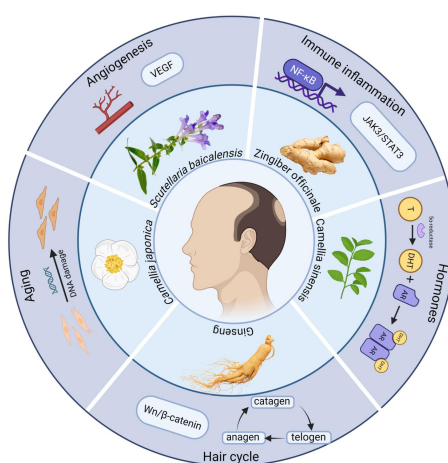
**Wnt/ $\beta$ -catenin signaling.** The Wnt/ $\beta$ -catenin pathway is essential for initiating anagen and maintaining HFSC proliferation. Activation of Wnt ligands stabilizes  $\beta$ -catenin, which translocates into the nucleus to upregulate target genes such as *LEF1*, *Axin2*, and *Cyclin D1* [31–33]. Therefore, targeting the Wnt/ $\beta$ -catenin signaling pathway could represent a key mechanism underlying the efficacy of TCM in treating hair loss. For instance, extracts from *Justicia procumbens* could promote the proliferation of human dermal papilla cells (hDPCs) and activate  $\beta$ -catenin signaling. In vivo studies using a testosterone-induced AGA mouse model further demonstrate that this extract improves hair shaft cuticle integrity, prolongs the anagen phase, and significantly upregulates  $\beta$ -catenin expression [34]. Active components in ginseng, such as ginsenoside Rg4, promote DP cell growth and extend the HF anagen phase by activating the AKT/GSK3 $\beta$ / $\beta$ -catenin signaling pathway in DP spheroids [35]. Leaf extract of *Gynostemma pentaphyllum* Makino induces hair growth through multiple mechanisms, including stimulating hDPCs proliferation, enhancing Wnt signaling pathway activity, and inhibiting the expression of hair loss-related gene TGF- $\beta$ 1 [36].

**BMP signaling.** The BMP signaling pathway plays a central role in the

growth, development, and cycle regulation of HFs, and its dysregulation is closely associated with various types of hair loss [37]. Researchers have identified more than 10 types of BMPs in vertebrates, among which BMP-2, BMP-4, and BMP-6 are related to HFs [38]. BMP2 is not expressed in the early stage but later shows a pattern of initially increasing and then decreasing with the HF cycle, whereas BMP4 is not expressed during the proliferation phase and is highly expressed during the regression phase [39, 40]. BMP6 inhibits the expression of Wnt10b, which serves as an activator in the transition of HFs from the resting phase to the growth phase [41]. BMP signaling acts as a “molecular brake”, and excessive BMP signaling may lead HF stem cells to remain excessively quiescent, delaying or inhibiting hair growth and resulting in hair loss. Studies have shown that the 95% ethanol extract of *Avicennia marina* may induce hair growth in the telogen phase by reducing BMP-4 protein in DPCs [42].

**Sonic hedgehog pathway.** Hair morphogenesis is closely related to Sonic hedgehog (Shh) signaling, and the activation of the Shh pathway as a downstream pathway of the Wnt/ $\beta$ -catenin pathway can induce proliferation of quiescent stem cells [43]. Hot water extract of *Thuja orientalis* has hair growth-promoting effects. Animal experiments have shown that local application of this extract to mice increases Shh protein levels, effectively inducing HFs to transition from the telogen to the anagen phase, prolonging the duration of the anagen phase, thereby increasing the number of HFs and enlarging follicle size, effectively treating hair loss [44].

In summary, the transition between HF cycle phases is orchestrated by a highly coordinated network of signaling pathways rather than by a single regulatory factor. Wnt/ $\beta$ -catenin signaling is indispensable for anagen initiation, driving activation and lineage commitment of HFSCs. This activity is functionally antagonized by BMP signaling, which enforces HFSC quiescence; thus, the dynamic balance between Wnt and BMP signaling establishes the threshold for hair cycle re-entry. Concurrently, Shh signaling is required for early anagen progression and downward follicular growth. Additional paracrine mediators, including VEGF, FGF-7 and FGF-10, support angiogenesis and epithelial-mesenchymal crosstalk necessary for sustained matrix cell proliferation. In contrast, TGF- $\beta$  and the Wnt antagonist DKK-1 promote catagen entry by inducing apoptosis and suppressing proliferative signaling. Therapeutic strategies, including traditional Chinese medicine-based interventions, are therefore thought to exert their effects by modulating this signaling equilibrium, enhancing pro-anagen pathways while attenuating inhibitory cues, to re-establish hair cycle homeostasis.



**Figure 1 Conceptual framework illustrating five major mechanisms underlying hair loss and the corresponding TCM-based therapeutic interventions.**

Each mechanism, hair follicle cycle disruption, androgen-hormone dysregulation, oxidative stress-associated aging, immune and inflammatory imbalance, and reduced angiogenesis, is paired with representative TCM strategies that modulate key molecular pathways involved in hair follicle regeneration. The figure was created with Biorender.

### Regulation of hormone levels

The pathological process of hair loss is closely related to the dynamic balance of hormone levels and signal regulation in the body. HFs, as hormone-sensitive organs, undergo precisely regulated cyclical growth, and the functional state of key cells such as DP cells and matrix cells is synergistically controlled by multiple hormonal signals [45]. Among these, androgens, particularly dihydrotestosterone (DHT), play a pivotal role in determining hair follicle fate. DHT binds specifically to androgen receptors (AR) in dermal papilla cells [46], activating downstream signaling pathways, suppressing DP cell secretion of hair growth-promoting factors such as VEGF and IGF-1, while upregulating factors like TGF- $\beta$  [47]. This results in follicle miniaturization, shortened anagen phase and prolonged telogen phase, ultimately leading to AGA.

**Inhibition of 5 $\alpha$ -reductase activity.** As a key rate-limiting enzyme regulating androgen metabolism, the expression and activity of 5 $\alpha$ -reductase are closely related to hormonal homeostasis and the growth fate of HF. Therefore, targeting 5 $\alpha$ -reductase is a crucial scientific entry point for understanding the pathogenesis of AGA. Accordingly, inhibition of 5 $\alpha$ -reductase activity reduces DHT levels and constitutes an established therapeutic strategy for hair loss. *Serenoa repens* (saw palmetto) extract exerts its anti-alpecia effects through a mechanism analogous to that of finasteride [48]: competitive inhibition of 5 $\alpha$ -reductase, which attenuates the testosterone-to-DHT conversion and thereby mitigates progressive hair follicle miniaturization [49]. *Stauntonia hexaphylla* extract is a 5 $\alpha$ -reductase inhibitor that can improve AGA by inhibiting 5 $\alpha$ -reductase and androgen signaling, as well as preventing apoptosis and premature catagen [50]. The main component of *Camellia sinensis* (green tea), epigallocatechin-3-gallate, stimulates human hair growth through promoting proliferation and anti-apoptotic effects on DP cells and also affects type I 5 $\alpha$ -reductase activity [51, 52].

**Regulation of hormone receptors and downstream signaling.** Herbal medicines not only alter androgen metabolism but also antagonize AR binding and downstream signaling. Network pharmacology predicts that major black ginseng constituents (deoxyoleanolic acid, ginsenosides Rb1, Rg3, and Rh4) engage multiple targets, including the AR. In mice, black ginseng extract reduced circulating testosterone and DHT while increasing estradiol, indicating broad hormonal rebalancing [53]. *Polygonum multiflorum* extracts have been shown to prevent hair loss by significantly reducing DHT-induced AR expression and eliminating androgen effects [54]. Combined use of aqueous extracts and polysaccharides from *Angelica sinensis* and *Platycladus orientalis* can treat AGA by targeting the AR and its Wnt/ $\beta$ -catenin signaling pathway [55].

### Delaying HF aging

HF aging is one of the important causes of hair loss, manifested by decreased function of HF stem cells, disordered HF cycles, and reduced regenerative capacity [56, 57]. With the intensification of global population aging, hair loss issues related to aging are becoming increasingly prominent. TCM shows unique advantages in combating HF aging, and its mechanisms mainly involve combating oxidative stress, regulating HF stem cell function, and improving the HF microenvironment.

**Antioxidant stress and reduction of oxidative damage.** Oxidative stress is one of the important mechanisms leading to HF aging. Reactive oxygen species (ROS) can damage the proliferation and migration of HF cells [58] and accelerate premature aging of HF cells [59]. Excessive ROS causes lipid peroxidation, protein carbonylation, and DNA lesions, leading to membrane damage, organelle dysfunction and programmed cell death. Within hair follicles, such oxidative stress impairs cellular integrity, induces apoptosis, and drives premature follicular aging [60]. Therefore, oxidative-stress modulation may represent a potential therapeutic mechanism in alopecia treatment [61]. Zhimo herbal extract is an aqueous extract of a herbal mixture. Its active components, sinapic acid and glabridin (S&G), can effectively alleviate oxidative stress caused by DHT, reduce levels of ROS and malondialdehyde, and increase the activity of glutathione

and superoxide dismutase [62]. Further studies found that the S&G combination inhibits ferroptosis through the  $\beta$ -catenin/TCF4/GPX4 axis. Ferroptosis is a novel iron-dependent form of cell death closely related to oxidative stress. In AGA, DHT induces ferroptosis in HF cells, while S&G treatment can reverse this process and protect HF cells from damage. In addition, the main active component of silymarin extract, silybin, promotes DPC proliferation by reducing the expression of ROS, iNOS, and COX2, reducing oxidative damage in cells and thus potentially contributing to the treatment of hair loss [63].

**Regulating HF cells' aging.** DPCs, located at the base of HFs, are important mesenchymal components that play a crucial role in promoting hair regeneration. In AGA, due to increased DHT levels and oxidative stress, DPCs undergo premature senescence, disrupting the normal hair follicle cycle [64]. Studies have shown that the main active components of *Camellia japonica* seed extract, camelliasaponins B1 and B2, can effectively inhibit DHT-induced premature senescence and DNA damage in DPCs by modulating the p16<sup>INK4a</sup>-pRb signaling pathway, thereby delaying the cellular aging process. Furthermore, this extract can directly activate HFSCs by downregulating p21 expression and restore the stem cell suppressive state mediated by aging DPCs [65]. *Ganoderma lucidum* (Lingzhi) contains more than 400 bioactive constituents—principally triterpenoids, polysaccharides, and peptides—conferring diverse pharmacological properties, including potent immunomodulatory and antioxidant activities [66]. Recent studies have also found that *Ganoderma lucidum* has potential in treating stress-induced hair loss, possibly through mechanisms related to delaying HF cells aging [67].

### Regulating inflammatory and immune balance

Inflammation and immune responses play a key role in various types of hair loss, such as AA and seborrheic dermatitis-related hair loss. Even in AGA, which is not directly associated with the immune system, inflammatory responses can exacerbate hair loss severity [68]. Therefore, addressing inflammation is crucial for successfully slowing the progression of hair loss. TCM, with its natural anti-inflammatory and immunomodulatory properties, can restore immune balance in HFs through multiple pathways, creating a microenvironment conducive to hair growth.

**Anti-inflammatory effects and regulation of inflammatory factors.** Various active components in TCM have significant anti-inflammatory effects. In the inflammatory pathogenesis of treating non-scarring alopecia (including AGA and telogen effluvium), interleukin-1 alpha, as a direct inhibitory factor of hair follicle growth, plays a key pathogenic role [69–71]. A study revealed that a compound preparation composed of six herbal extracts (*Urtica Dioica* Root Extract, *Urtica Urens* Leaf Extract, *Equisetum Arvense* Leaf Extract, *Achillea Millefolium Aerial Part* Extract, *Matricaria Chamomilla* Flower Extract and *Ceratonia Siliqua* Fruit Extract) can significantly downregulate interleukin-1 alpha gene expression levels, suggesting that it has the potential to treat non-scarring alopecia by targeting this key inflammatory mediator [71]. Curcumin is a well-known anti-inflammatory compound, playing a significant role in reducing pro-inflammatory factors while increasing the release of anti-inflammatory factors [72]. Research indicates that curcumin controls chronic inflammation by inhibiting inflammatory pathways such as NF- $\kappa$ B and COX-2, thereby reducing the production of inflammatory mediators like prostaglandins and leukotrienes. For the scalp, this anti-inflammatory effect helps to reduce peribulbar inflammatory infiltration and protect HFs from inflammatory damage. It has been shown that treatment of mice with *Angelica gigas Nakai* extract and its main active component, decursin, significantly promotes hair growth by reducing pro-inflammatory cytokine levels and increasing anti-inflammatory cytokine levels [73].

**Immune regulation and the JAK-STAT pathway.** The JAK-STAT signaling pathway plays an important role in immune regulation and the HF cycle. Overactivation of the JAK-STAT pathway can lead to inflammatory hair loss [74]. Research has found that curcumin can effectively inhibit the JAK-STAT signaling pathway, particularly

JAK3, with an effect similar to small molecule JAK inhibitors [72]. This discovery provides a scientific basis for the use of curcumin in treating inflammatory and autoimmune hair loss. The active components in *Ganoderma lucidum* have also been shown to possess immunomodulatory effects. *Ganoderma lucidum* polysaccharides potentiate innate immunity by activating macrophages and dendritic cells, whereas its triterpenoids modulate T-cell responses, collectively restoring immune homeostasis [66]. This immunomodulatory effect may have therapeutic significance for autoimmune hair loss, such as alopecia areata. Additionally, the cedaryl derived from *Zingiber officinale* (ginger) can treat AA through oral administration. The core mechanism lies in inhibiting the JAK3/STAT3 signaling pathway, alleviating immune suppression, activating the Wnt/ $\beta$ -catenin pathway and inhibiting the apoptosis of HF cells, thereby promoting hair follicle regeneration and hair restoration [75].

#### Promoting HF angiogenesis and blood flow supply

Adequate blood supply and nutrient delivery are crucial for the growth and maintenance of HFs. DP cells, the central command center of the HFs, trigger apoptosis upon DHT challenge, and associated vascular regression creates a hypoxic, nutrient-poor microenvironment [47]. Herbal medicines reverse this process by promoting angiogenesis and improving perifollicular blood flow via diverse mechanisms, thus ensuring sufficient oxygen and nutrient supply for follicle viability.

**Upregulation of vascular endothelial growth factor.** As an organ highly dependent on blood supply, the precise regulation of the cyclic growth of HFs relies heavily on the stability and dynamic balance of the vascular microenvironment surrounding them. Among these, DP cells of the HF serve as the core regulators of HF growth signaling. The maintenance of their proliferation, differentiation, and secretory functions depends on adequate blood oxygen and nutrient supply, with VEGF being a key factor that promotes angiogenesis. The ethanol crude extract of *Centella asiatica* is rich in phenols and flavonoids, and can safely and effectively promote the growth of human HF cells by upregulating the VEGF gene, showing potential for hair growth [76]. The flavonoid compound baicalin in *Scutellaria baicalensis* promotes hair growth by inducing the mRNA expression of VEGF, thereby regulating the activity of DP cells to promote hair growth [77]. The TCM formula Shen-Ying-Yang-Zhen formula (SYF) shows potential as a preventative treatment for hair loss by improving oxidative stress and angiogenesis around the HFs in AGA [78]. In a DHT-treated hDPC model, SYF upregulated VEGF expression and significantly promoted perifollicular angiogenesis.

**Activation of pro-angiogenic signaling pathways.** TCM can also activate multiple pro-angiogenic signaling pathways. The MAPK pathway is a multi-layered kinase signaling cascade that plays an important role in cell physiology, including cell differentiation, proliferation, cell death, and inflammation [79]. Research has found that Qu-shi-yu-fa Decoction can promote angiogenesis around HFs by activating the PI3K-Akt and MAPK signaling pathways. After treatment with Qu-shi-yu-fa Decoction, the activation levels of PI3K and AKT in the dorsal skin of AGA model mice were significantly increased, and the phosphorylation levels of MEK and ERK were also significantly elevated [80], indicating that the MAPK signaling pathway was activated. Similarly, in mice treated with black ginseng extract, VEGF expression in the skin increased while TGF- $\beta$  expression decreased. Network pharmacology analysis identified that black ginseng extract may exert its effects by regulating targets such as AR and signaling pathways like MAPK [53].

Shikimic acid (SA) was originally known as an extract obtained from *Illicium anisatum* (Japanese star anise) and *Illicium verum* (Chinese star anise). According to reports, SA treatment enhances the phosphorylation of p38 and CREB in hDPCs, suggesting that SA can increase the expression of growth factors (c-myc, HGF, KGF, and VEGF) through the MAPK/CREB pathway, which in turn significantly promotes the proliferation of hDPCs [81]. *Morus alba* L. root extract acts on dermal fibroblasts to promote the secretion of pro-angiogenic factors such as VEGF; these paracrine factors not only enhance the

tubular structure formation and migration abilities of vascular endothelial cells to improve microcirculatory blood supply around HFs, but also activate the ERK/AKT signaling pathways related to hair growth in DPCs of HFs, upregulating the expression of growth-promoting genes such as IGF-1 [82].

**Improving microcirculation and hemorheology.** HF growth and cyclic turnover are regulated by the skin microenvironment, which comprises diverse cell types and signaling molecules secreted by tissues and cells [83]. TCM can also enhance the nutritional supply to HFs by improving microcirculation and hemorheological properties. *Rosmarinus officinalis* L. is a well-known herbal plant that has been widely studied due to its various applications in the food and pharmaceutical industries [84].

Rosemary oil has important ingredients, including caffeic acid, rosmarinic acid, 12-methoxycarnosic acid, and camphor. Studies have shown that the hair growth-promoting properties of Rosemary oil are believed to be related to its ability to enhance microcapillary blood flow [85]. *Terminalia bellirica* (Gaertn.) Roxb is a traditional Tibetan medicine that contains various active substances, such as chebulic acid, tannic acid, gallic acid, andrographolide, tectorigenin lignans, and tannins. Studies have found that it can remodel the HF microenvironment by reducing oxidative stress and promoting angiogenesis [86].

### Mechanistic links between classical TCM theory and molecular pathways

Pathological hair loss is therefore viewed in traditional Chinese medicine as an external manifestation of internal imbalance. Common patterns include liver–kidney deficiency, characterized by insufficient essence and blood to nourish the hair; Qi and blood deficiency, reflecting inadequate nourishment of the hair follicles; and obstruction by pathogenic factors such as dampness-heat, blood stasis, or phlegm-dampness.

Contemporary molecular biology now enables systematic reinterpretation of these classical concepts in terms of cellular metabolism, oxidative stress, microvascular regulation, and hormonal homeostasis. By delineating shared mechanistic nodes, this framework bridges canonical TCM syndrome patterns with defined modern signaling pathways (Table 1).

#### Liver and kidney deficiency—stem cell exhaustion and hormonal dysregulation

The TCM concept of “kidney essence” reflects intrinsic regenerative and reproductive potential, paralleling stem cell activity and endocrine balance. It clinically manifests as chronic/age-related hair loss. Classical kidney-tonifying herbs such as *Polygonum multiflorum*, *Rehmannia glutinosa*, and *Panax ginseng* might activate VEGF and FGF pathways, recreating a supportive niche for follicular regeneration [87, 88]. These findings provide mechanistic grounding for the concept that replenishing kidney essence supports hair regeneration.

#### Qi and blood deficiency—impaired microcirculation and energy metabolism

“Qi” represents functional energy, including metabolic and circulatory activity. “Blood deficiency” suggests poor perfusion and oxygen/nutrient delivery to tissues. Clinically, it presents as diffuse hair thinning. *Angelica sinensis* and *Ligusticum chuanxiong*, classical blood-nourishing and circulation-promoting herbs, potentially induce VEGF and KGF expression, improving oxygen delivery to the hair follicle and prolonging anagen maintenance [89].

#### Blood stasis and Qi stagnation—local hypoxia, inflammation, and fibrosis

“Blood stasis” in TCM describes impaired blood flow and accumulation of stagnant elements, often manifesting as localized pain or discoloration. In scalp pathology, this mirrors microvascular dysfunction, fibrosis, and chronic inflammation that impede follicle

renewal. Blood stasis is reflected by upregulation of TGF- $\beta$ 1, collagen I/III, and  $\alpha$ -SMA, leading to perifollicular fibrosis. Such remodeling restricts HFSC activation, akin to follicular sclerosis observed in long-standing AGA. Herbs like *Salvia miltiorrhiza* (Danshen) and *Ligusticum chuanxiong* exhibit potentially anti-fibrotic properties via inhibition of TGF- $\beta$ /Smad and JAK-STAT [90, 91], reducing inflammatory cytokine release and extracellular matrix (ECM) deposition.

#### Damp-Heat accumulation—seborrhea, microbial dysbiosis, and oxidative stress

The “damp-heat” syndrome corresponds clinically to seborrheic dermatitis-related alopecia and inflammatory scalp conditions. In biomedical terms, this reflects sebaceous gland hyperactivity, Malassezia overgrowth, and oxidative stress. Excess sebum and lipid peroxidation generate ROS, disrupting follicular integrity and triggering inflammation [92]. Herbs used to “clear heat and remove dampness” (e.g., *Sophora flavescens*) possess antibacterial and antioxidant effects [93]. For example, *Sophora flavescens* alkaloids suppress NF- $\kappa$ B [94].

#### Heat in blood and wind attack—autoimmunity and inflammatory cytokine activation

“Heat in the Blood” signifies hyperinflammatory states, while “Wind attack” implies sudden onset and migratory symptoms, analogous to acute autoimmune processes such as AA. Classical “blood-cooling and wind-dispelling” herbs such as *Rehmannia glutinosa*, *Glycyrrhiza uralensis*, and *Scutellaria baicalensis* inhibit JAK/STAT signaling and

mediate broad immunosuppressive and anti-inflammatory effects [95–97]. Baicalin from *S. baicalensis* inhibits STAT3 phosphorylation and potentially reduces IFN- $\gamma$  production [96], while glycyrrhizin suppresses HMGB1 signaling [98], potentially protecting the immune privilege of hair follicles.

### Traditional Chinese medicine formulas and clinical evidence in alopecia treatment

Hair loss is mainly attributed to deficiencies in kidney essence, liver qi stagnation, and blood deficiency. Secondary factors such as damp-heat accumulation, blood stasis, and wind pathogen invasion/wind attack also contribute to the pathology. A recent meta-analysis concluded that TCM used as adjunct therapy can increase the overall efficacy rate for AGA compared with controls, but emphasized the need for higher quality RCTs and standardized endpoints [99]. TCM formulas for alopecia reflect a holistic therapeutic strategy combining internal nourishment and external stimulation. Herbs such as *Platycladus orientalis* [51], *Polygonum multiflorum* [54], and topical Shen Bai hair growing decoction [12] act on diverse biological targets—ranging from DHT inhibition and antioxidant defense to Wnt activation and angiogenesis. Modern pharmacological evidence supports their ability to restore the follicular microenvironment and delay hair follicle senescence. Continued integration of clinical research with systems pharmacology will further clarify their role in evidence-based evaluation of safety and efficacy in alopecia treatment [99] (Table 2).

**Table 1 A conceptual bridge emerges between holistic theory and hair follicle biology**

TCM syndrome	Modern biological indicators	Clinical manifestation	Biological correspondence	Representative mechanisms / Pathways	Key herbs	Ref.
Liver–Kidney deficiency	↑MDA	Chronic/aging alopecia	Stem cell exhaustion, DPC senescence	↓Wnt/ $\beta$ -catenin, ↓FGF7/IGF-1	<i>Polygonum multiflorum</i> , <i>Rehmannia</i> ,	[87, 88]
Qi–Blood deficiency	↓Scalp capillary density, ↓tissue oxygenation	Diffuse hair thinning	↓VEGF	VEGF/eNOS/HIF-1 $\alpha$ pathway	<i>Angelica sinensis</i> , <i>Ligusticum chuanxiong</i>	[89]
Blood stasis–Qi stagnation	↓Local tissue oxygenated hemoglobin	Local ischemic scalp, fibrosis	TGF- $\beta$ activation, ECM accumulation	↓NF- $\kappa$ B, ↓Smad2/3 ↓ $\alpha$ -SMA	<i>Salvia miltiorrhiza</i> , <i>Chuanxiong</i>	[90, 91]
Damp–heat accumulation	↑Sebum production, ↑IL-1 $\beta$ , TNF- $\alpha$ ,	Oily scalp, dandruff, itching	Sebum oxidation, microbial imbalance	↓NF- $\kappa$ B, ↓ROS	<i>Sophora flavescens</i>	[92, 94]
Heat in Blood–Wind attack	↑IL-1 $\beta$ ↑ROS	Sudden shedding, AA	Autoimmunity, cytokine storm	↓STAT1/3, ↓IFN- $\gamma$ , ↓TLR4	<i>Scutellaria</i> , <i>Rehmannia</i> , <i>Glycyrrhiza</i>	[95, 98]

AA, alopecia areata.

**Table 2 Commonly used TCM herbs, active ingredients and hair-growth related pharmacological effects**

Herb (Latin name)	Major active compounds	Pharmacological actions related to hair growth	Ref.
<i>Platycladus orientalis</i> (L.) Franco	Flavonoids (orientin, isoorientin), diterpenoids	Inhibits 5 $\alpha$ -reductase, enhances dermal papilla proliferation, anti-inflammatory and antioxidant	[51]
<i>Polygoni multiflori radix</i>	2,3,5,4'-tetrahydroxystilbene-2-O- $\beta$ -D-glucoside (THSG)	Promotes dermal papilla proliferation via Wnt/ $\beta$ -catenin; antioxidant; delays DPC senescence	[54]
Topical Shen Bai hair growing decoction	Mainly organic acids and quinones	Suppresses TNF- $\alpha$ and IL-6 levels and improve pathological phenomena	[12]
<i>Angelica sinensis</i>	Ferulic acid, ligustilide	Enhance VEGF	[89]
<i>Panax ginseng</i>	Ginsenosides (Rg1, Rb1, Rg3)	Promote DP cell growth and extend the HF anagen phase by activating the AKT/GSK3 $\beta$ / $\beta$ -catenin signaling pathway	[35]

Table 3 Summary of representative clinical trials on TCM for alopecia

Registry ID	Condition	Intervention	Phase / Design
ChiCTR2500109418	AGA	Wash hair with Dansi lotion	/, Randomized, Parallel, Controlled
ChiCTR1900024832	AGA	TCM hair growth fluid combined with micro-needle treatment	Phase 0, Randomized, Parallel, Controlled
ChiCTR2400083966	AA	Conventional western medicine treatment combined with Shen-Ying-Yang-Zhen Dan and Hai-Ai-Tang	/, Randomized, Parallel, Controlled
ChiCTR2100047194	AA	Shaoyao-Gancao Decoction	Phase 0, Single arm
ChiCTR1800018691	AA	Two 25-mg oral tablets of compound glycyrrhizin three times per day and topical 0.05% halometasone cream locally twice daily	Phase 4, Randomized, Parallel, Controlled

AGA, androgenetic alopecia; AA, alopecia areata.

### Synergistic dynamics of herbal pairings in alopecia formulas

Synergistic interaction often manifests as "convergent targeting," where different herbs within a pairing modulate multiple nodes within the same signaling cascade. For example, Dahuang-Gancao herb pair demonstrates that this combination synergistically promotes the transition of HFIs from the telogen to the anagen phase. While Dahuang activates  $\beta$ -catenin-mediated transcriptional activity, Gancao constituents further stabilize the Wnt/ $\beta$ -catenin signaling cascade by inhibiting its endogenous antagonists, thereby significantly lowering the activation threshold for HFSC proliferation [100].

### Summary of registered clinical trials

To assess the current clinical landscape of TCM for alopecia, we summarized registered trials from the Chinese Clinical Trial Registry (ChiCTR). These trials primarily focus on AGA and AA, exploring diverse interventions ranging from oral decoctions and topical herbal applications to acupuncture and integrated therapies (Table 3).

### Limitations in clinical research design

Despite increasing clinical interest in TCM for alopecia management, substantial methodological limitations persist in the existing body of clinical evidence [101, 102]. Firstly, most clinical studies are limited by small sample sizes, single-center designs, and inadequate statistical power, which restrict the generalizability and reproducibility of reported outcomes. Many trials enroll fewer than 100 participants and lack appropriate sample size calculations, increasing the risk of type I and type II errors. Second, the absence of rigorous control groups remains a major concern. A considerable proportion of studies are non-randomized, open-label, or lack placebo or active comparators, making it difficult to distinguish true therapeutic effects from placebo responses or natural disease fluctuation. This limitation is particularly relevant in alopecia, where spontaneous remission and psychological factors can substantially influence outcomes. Third, heterogeneity in diagnostic criteria and patient stratification undermines cross-study comparability [101]. Variations in alopecia subtype classification (e.g., androgenetic alopecia vs. mixed-pattern hair loss), disease severity grading, and inclusion criteria frequently lead to heterogeneous study populations, obscuring treatment-specific effects. Fourth, outcome measures are often subjective, non-standardized, or insufficiently validated [103]. Many studies rely primarily on investigator- or patient-reported outcomes without incorporating objective endpoints such as phototrichogram analysis, hair density quantification, hair shaft diameter measurement, or standardized global photography. In addition, follow-up durations are often short, limiting assessment of sustained efficacy and relapse rates. Fifth, inadequate standardization of herbal formulations and dosing regimens complicates interpretation of clinical efficacy [103].

Differences in herb composition, extraction methods, dosage, treatment duration, and route of administration (oral vs. topical) are frequently observed even for identically named formulas, thereby impairing reproducibility and dose-response assessment. Finally, mechanistic endpoints are rarely integrated into clinical trial design. Most studies [101] focus exclusively on clinical outcomes without incorporating biomarker analyses, scalp biopsy assessments, or molecular readouts that could link clinical responses to underlying biological mechanisms. This disconnect limits causal inference and hampers translation from clinical observation to mechanism-driven optimization. These limitations highlight the urgent need for well-designed, randomized, double-blind, placebo- or active-controlled trials with standardized diagnostic criteria, objective outcome measures, rigorous quality control of herbal preparations, and integration of mechanistic biomarkers. Addressing these issues will be essential for advancing TCM-based therapies from empirical application toward evidence-based clinical practice in alopecia [101, 103].

## Research challenges and future directions

### Complexity and standardization of herbal formulations

A major challenge in the scientific validation of TCM for alopecia lies in the complexity and variability of herbal formulas. Although TCM is based on natural sources, some herbs do pose potential risks, such as liver toxicity. Traditional processing techniques (*paozhi*) for Chinese herbs can reduce toxicity and enhance efficacy by altering the chemical composition of the ingredients [104]. For example, with *Polygonum multiflorum*, processing changes the level of anthraquinones, significantly reducing its liver toxicity [105]. Each TCM prescription typically contains multiple herbs, each with dozens of active phytochemicals that vary according to species, geographical origin, harvest season, and processing methods [106–108]. Furthermore, lack of standardized extraction and quality control protocols impairs reproducibility among studies. Even within the same-named formula, proportions and preparation methods often differ between institutions or practitioners. Establishing standardized fingerprints using HPLC, LC-MS, or metabolomics is therefore essential to ensure consistency and reliability.

### Integrative landscape: the TCM syndrome-pathway-target axis

The clinical efficacy of TCM in alopecia is rooted in its ability to modulate the systemic biological state, termed "Syndrome" (Zheng), which represents a specific cluster of molecular dysregulations. TCM interventions act on the dynamic nexus of TCM syndrome patterns-biological pathways-therapeutic targets to restore the

homeostasis of the HF microenvironment.

**Liver-Kidney deficiency: stem cell senescence and Wnt/ $\beta$ -catenin exhaustion.** In canonical TCM theory, "Liver and Kidney deficiency" denotes a systemic decline in intrinsic regenerative capacity. At the molecular level, this syndrome is biologically synonymous with HFSC exhaustion, androgen-mediated senescence, and the dampening of the Wnt/ $\beta$ -catenin signaling cascades. Mechanistic studies have confirmed that restoration of Wnt activity is indispensable for HFSC activation and anagen re-entry [109]. For instance, recent evidence reveals that the Dahuang-Gancao decoction and specific botanical compounds dynamically rescue DPCs from premature catagen entry by promoting  $\beta$ -catenin nuclear translocation and stimulating HFSC proliferation, thereby reversing androgen-driven senescence [100].

**Qi-Blood Stasis: microvascular uncoupling and  $\text{tgf-}\beta$ -mediated fibrosis.** The "Qi and Blood stasis" pattern clinically corresponds to perifollicular microvascular dysfunction and extracellular matrix remodeling. Biologically, this state is characterized by local hypoxia, downregulated VEGF expression, and the hyperactivation of TGF- $\beta$ -mediated fibrosis, which mechanically restricts HF expansion. Botanical agents designed to invigorate blood circulation (e.g., *Ginkgo biloba flavones* and *Salvia miltiorrhiza*) reverse these fibrotic constraints. Recent pharmacological validations confirm that these extracts fundamentally remodel the follicular niche by downregulating TGF- $\beta$  expression and upregulating the VEGF-A signaling axis [90, 110]. This mechanically relieves follicular compression and drives angiogenesis, re-establishing the vascular niche essential for robust anagen maintenance.

**Damp-Heat and Blood Heat: collapse of HF immune privilege.** Conversely, "Damp-Heat" and "Heat in the Blood" syndromes align with acute inflammatory and autoimmune phenotypes, driving the pathology of alopecia areata (AA) and inflammatory shedding. These hyper-reactive states are molecularly driven by the collapse of hair follicle immune privilege (HF-IP), mediated by IFN- $\gamma$  and the aberrant hyperactivation of the JAK-STAT signaling cascades [6]. Multi-target botanical agents structurally intervene by inhibiting STAT3 phosphorylation and reducing Th1/Th17 cytokine production. This targeted immunosuppression effectively quenches perifollicular inflammation, restoring the compromised immune privilege of the hair bulb [6, 66].

Hence, TCM formulas do not merely alleviate symptoms; they orchestrate a systems-level rewiring of the follicular microenvironment, demonstrating profound therapeutic synergy.

#### Mechanistic complexity and multi-target effects

Unlike synthetic drugs that act on single molecular targets, TCM formulas exert multitarget, multi-pathway regulatory effects—modulating oxidative stress, inflammatory cytokines, endocrine balance, and microcirculation simultaneously [111]. While this network-based action aligns with the multifactorial nature of alopecia, it also complicates mechanistic elucidation.

To overcome this, systems biology and network pharmacology approaches have been increasingly used to map herb-compound-target-pathway interactions [112]. However, these computational predictions require experimental validation—for instance, using organoid cultures of human hair follicles or single-cell RNA sequencing to trace pathway-specific responses in dermal papilla and follicular stem cells [113].

#### Conclusion

Alopecia is a disorder characterized by its complexity and multifactorial nature. The underlying causes of this condition are multifaceted, including dysregulation of hair follicle cycling, impaired stem cell activation, inflammatory microenvironments, hormonal influences, and disruptions in key signaling pathways such as Wnt/ $\beta$ -catenin, PI3K/Akt, JAK/STAT, and TGF- $\beta$ . The current therapeutic options available are limited by a number of factors, including their partial efficacy, the occurrence of adverse reactions,

and a lack of multi-target action. In this context, TCM offers a compelling therapeutic paradigm, characterized by its multi-component, multi-pathway regulatory properties that align naturally with the biological complexity of hair follicle pathology.

However, the current body of evidence is not yet conclusive. A significant number of studies have been found to rely on small sample sizes, non-standardized herbal preparations, or incomplete mechanistic validation. The heterogeneity of herbal formulas, variability in extraction methods, and the paucity of high-quality randomized controlled trials continue to limit the clinical translation of TCM in the management of alopecia. Moreover, the majority of studies examine individual herbs or compounds, which do not fully capture the synergistic nature of classical TCM formulations.

In order to bridge the gap between traditional practice and modern evidence-based medicine, there is a necessity to integrate standardized herbal profiling, multi-omics technologies, advanced delivery systems (e.g., microneedles [114], nanoparticles [115]), and high-quality clinical trial design. A more profound comprehension of the intricate interplay between herbs, pathways and phenotypes is poised to enhance the efficacy of therapeutic strategies and facilitate the identification of lead molecules or optimized combinations for drug development. TCM treats hair loss through the synergistic action of multiple targets and pathways, demonstrating a unique advantage in overall regulation. This mechanistic integration reframes the complex pathology of hair loss and provides a solid foundation for multi-target natural therapies, potentially transforming treatment from single-pathway drugs to holistic, systems-level regulation. In summary, TCM offers a comprehensive and biologically plausible framework for the development of multi-target therapies for alopecia. By integrating traditional knowledge with contemporary molecular and clinical methodologies, future research endeavors can more effectively leverage the therapeutic potential of TCM to develop safe, effective, and mechanistically informed treatments for hair loss.

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