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Review

# Mechanism of action of herbs and their active constituents used in hair loss treatment☆

Anna Herman [a,*], Andrzej P. Herman [b]

[a] Faculty of Cosmetology, The Academy of Cosmetics and Health Care, Podwale 13 street, 00-252 Warsaw, Poland
[b] Laboratory of Molecular Biology, The Kielanowski Institute of Animal Physiology and Nutrition, Polish Academy of Sciences, Instytucka 3 street, 05-110 Jabłonna, near Warsaw, Poland

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ABSTRACT

This article discusses the mechanisms via topically applied products containing herbs and their active constituents affect the hair growth process. It was reported that the mechanisms involving (1) insulin-like growth factor-I (IGF-I), (2) vascular endothelial growth factor (VEGF), (3) epidermal growth factor (EGF), (4) fibroblast growth factor 2 (FGF-2), (5) endothelial nitric oxide synthase (eNOS), (6) Wnt/β-catenin signalling pathway, (7) prostaglandin E (PGE), (8) prostaglandin F (PGF) stimulate hair growth, whereas the mechanisms engaging (1) 5α-reductase and dihydrotestosterone (DHT), (2) transforming growth factor beta (TGF-β), (3) fibroblast growth factor 5 (FGF-5), (4) prostaglandin $D_2$ ($PGD_2$) inhibit hair growth. The knowledge summarized in the paper may be an inspiration to create new preparations for the treatment of hair loss.



**Contents**



☆ Abbreviations: 5α-reductase; dihydrotestosterone; prostaglandin; vascular endothelial growth factor; insulin-like growth factor-I; transforming growth factor β; Wnt/β-catenin signaling pathway; fibroblast growth factor; epidermal growth factor; nitric oxide synthase.

* Corresponding author at: Podwale 13 street, 00-252 Warsaw, Poland.
*E-mail address:* anna.herman@onet.pl (A. Herman).

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## 1. Introduction

Androgenetic alopecia (AGA) and alopecia areata (AA) are common forms of hair loss. AGA is caused by the heightened sensitivity of scalp follicles to dihydrotestosterone (DHT) whereas AA is induced by an autoimmune reaction [1]. Various synthetic medicines are available for hair loss treatment. Among them are minoxidil, finasteride and spironolactone used for AGA treatment, as well as minoxidil, anthralin (dithranol), corticosteroids and tretinoin used for AA therapy [1,2,3]. The mechanisms by which synthetic drugs promotes hair growth are partially understood. Minoxidil has a specific direct effect on the proliferation and differentiation of follicular keratinocytes which leads to prolongation of the anagen phase. Many mechanisms of action of minoxidil have been proposed [4], including (1) minoxidil metabolised by the enzyme sulphotranspherase to minoxidil sulfate in the hair follicles, acts as a potassium channel agonist to reduce the cytoplasmic free $Ca^{2+}$ concentration and then prevents epidermal growth factor (EGF) from inhibiting hair formation [5,6], (2) minoxidil increased expression of VEGF and its receptors in the dermal papilla which subsequently stimulates angiogenesis in the hair anagen phase [7], (3) minoxidil stimulates regrowth in hair follicle cultures where a blood supply is absent [8], (4) minoxidil is a potent activator of prostaglandin endoperoxide synthase-1, a cytoprotective enzyme that stimulates hair growth [9], (5) minoxidil induce hair growth through the activation of Wnt/β-catenin pathway [10], (6) minoxidil increases the number of DNA synthesising cells in the dermal papilla, bulbar matrix, outer root sheath and perifollicular fibrocytic cells, what result in the prolongation of anagen phase and the conversion of vellus hairs to terminal hairs [11,12]. In turn, finasteride is a competitive inhibitor of type II 5α-reductase. This intracellular enzyme converts testosterone into the biologically more active metabolite dihydrotestosterone (DHT) which binds to androgenic receptors in the hair follicle and then activates the genes responsible for hair follicle regression. By reducing scalp tissue levels of DHT, finasteride treatment suppresses male pattern hair shedding [13,14]. Dutasteride mechanism of action is similar to finasteride, with one difference, dutasteride is a competitive inhibitor both of type I and II 5α-reductase [15]. Spironolactone has potent *anti*-androgenic properties resulting from dual mechanisms: reduction of androgen production and competitive blockage of androgen receptors in target tissues [16]. The mechanism of anthralin action is unknown, but in mouse studies anthralin has been shown to decrease the expression of tumor necrosis factor-α (TNF-α) and -β (TNF-β) in the treated area [17].

In recent years, many herbal topical formulations have been marketed worldwide to prevent hair loss or promote hair growth. There are many advantages of using these natural drugs including patient compliance, less side-effects, easy availability, low-cost and more than one mode of biochemical action for hair loss treatment. Therefore, the aim of this study was summarize current knowledge regarding mechanism of action of topically used herbal products for hair loss treatment.

## 2. Methods

### 2.1. Search strategy

The PubMed, Scopus and Google Scholar databases were searched for articles published from 2000 to the present. Search terms included "herbal products for hair loss", "herbal products for hair growth", "herbal treatments for androgenetic alopecia", "herbal treatments for alopecia areata", "topical herbal medication for androgenetic alopecia " and " topical herbal medication for alopecia areata". References from reviews about herbal products and alopecia were searched for additional articles and case reports. A manual search was also conducted based on citations in the published literature.

### 2.2. Inclusion and exclusion criteria

Selection criteria included articles that examined topically used herbal products for the treatment of alopecia based on animal and human trials with biochemical analysis on their mechanism of action. Other than the topical administration (e.g. oral, systemic) of herbal products in alopecia treatment were excluded from the study. Also publications in a languages other than English were excluded.

## 3. Transfollicular penetration of herbs and their active constituents used for hair loss treatment

The transfollicular administration of pharmacologically active molecules is recognised as a significant element for therapeutic interest, mainly with regard to delivery to specific sites of the hair follicle and the reduction of hepatic metabolism and systemic toxicity [18]. Moreover, hair follicles are privileged pathways for topically applied formulations with specific compounds, which enter faster into these shunts than through the stratum corneum, a main skin barrier [19]. The hair follicle itself can be divided into at least four target areas for topical application: (1) the sebaceous gland, (2) the bulge region, (3) the hair matrix cells and (4) the hair follicle infundibulum [20]. The latter provides an interrupted barrier with increased permeability and is surrounded by a high density of immune cells and an extensive capillary network important for penetration and systemic absorption of active agents [21]. Topically applied active compounds from herbal products must be able to penetrate epidermal barrier and reach the specific sites of the hair follicles to affect hair growth via different biological pathways. Teichmann et al. [22] and Lademann et al. [23] demonstrated that a 2 minute contact between the shampoo with caffeine and the skin surface was sufficient for its penetration deeply into the hair follicles and remains there for up to 48 h, even after hair washing. This demonstrates the long-term reservoir function of the hair follicles for topically applied substances such as caffeine. Moreover, caffeine inhibits the activity of the 5α-reductase and leads to a significant stimulation of human hair follicle growth in vitro [24]. Despite caffeine, a large number of active components produced by plants is not able to pass through the skin barrier. Lipid solubility and molecular size are the major limiting factors for phytomolecules to pass the biological membrane after topical application. Therefore, the use of novel drug delivery systems containing herbal formulation has enhanced the therapeutic effects of plant extracts and facilitates their penetration through the skin [25]. Mixture of *Aloe vera* gel (1%) and *Apium graveolens* ethanolic extract (2%) in the form of O/W microemulsion was effective in penetrating into the pilosebaceous gland and showed the highest hair growth promoting activity [26]. Lipophilic curcumin (hair growing agent) incorporated in O/W microemulsion and in an amphiphilic cream was detected in human follicular infundibula and follicular orifices, respectively [27]. Monoolein cubosomal suspension (1%) containing 3% herbal extracts mixture (*Poria cocos, Thuja orientalis, Espinosilla, Lycium chinense Mill, Coix lacryma-jobi, Polygonum multiflorum Thunberg*) significantly enhances the skin permeation of the herbal extracts as potent as minoxidil solution (2.4%) [28]. Among them *T. orientalis*, *P. multiflorum* and *Espinosilla* extract showed hair growth promoting efficacy. Hair growing ingredients - hinokitiol loaded in monoolein cubosome revealed much higher skin permeation than hinokitiol dissolved in water, even the concentration of hinokitiol in cubosome suspension was lower than the concentration in the aqueous solution [29]. Ding et al. [30] showed that penetration of the flavonoid-rich *Allium cepa* leaf extract encapsulated in β-cyclodextrin proceeds across skin via both follicular and transcellular routes. Tsujimoto et al. [31] found that the dispersion liquids containing hair growing ingredient (hinokitiol, glycyrrhetinic acid) encapsulated in poly(lactic-*co*-glycolic acid) (PLGA) nanospheres exerted human scalp-pore permeability 2.0- to 2.5-fold higher than samples containing only the hair growing ingredients. Moreover, the hair growing effect of the encapsulated PLGA nanospheres was improved in the in