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# Cell regeneration in the therapy of androgenic alopecia

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**ABSTRACT**

This article discusses a promising method of treating androgenic alopecia using plant-derived growth factors. Androgenic alopecia is one of the most common causes of baldness in men and women, and traditional treatments such as drug therapy and hair transplantation do not always provide long-term effects. In recent years, plant growth factors have attracted attention due to their regenerative properties and ability to stimulate hair growth. This article presents the results of clinical studies as well as the mechanisms of action of plant growth factors on hair follicles and their regeneration in androgenic alopecia.

***Keywords:*** *androgenic alopecia, plant stem cells, hair follicles*

## 1. INTRODUCTION

Androgenetic alopecia is a genetically predetermined hair loss caused by an overreaction of hair follicles to androgens. This condition affects up to 50% of men and 30% of women in their 50s and is characterized by progressive loss of terminal hair after puberty. It has a characteristic distribution in both men and women. Hair loss is most prominent in the parietal and frontal temporal regions in men. In women, the frontal line of hair growth is usually preserved with diffuse hair loss on the scalp and top of the head, with loss often marked by a broader central portion [1].

Testosterone and other weaker androgens such as dehydroepiandrosterone and androstenedione are metabolized in many skin tissues. Testosterone can freely pass through the cell membrane and is converted in the cytoplasm to dihydrotestosterone (DHT) by 5 α-reductase (mainly type II). DHT binds firmly to the androgen receptor (AR) and this complex is translocated into the nucleus by AR coactivators. This leads to transcription of the target gene and eventually translation into genes that exhibit biological activity. [2]. The concentration of DHT along with 5 α reductase and androgen receptors increases in balding scalp. Other enzymes involved in the conversion of weak androgens to strong androgens are 3 β hydroxysteroid dehydrogenase (3 β HSD) and 17 β hydroxysteroid dehydrogenase (17 β HSD), which also show increased activity in AGA. The higher the concentration of androgen and androgen receptors, the greater the effect on the expression of genes that control the follicular cycle [3].

Understanding of hair follicle biology over the past 20 years has established the fundamental role of the dermal papilla in maintaining hair growth, with multipotent epithelial stem cells of the dermal papilla inducing proliferation and differentiation. Other autocrine, paracrine factors and signaling pathways are also involved in this cross-talk between dermal papillae and hair follicle "Bulger zone" stem cells.

The cross-talk between dermal papillae and hair follicle cells that unfolds under the influence of androgens results from the secretion of many factors from the dermal papillae. They have an autocrine action on the dermal papillae themselves and a paracrine action on the epithelial cells of the hair follicle [4]. These factors include growth factors such as insulin-like growth factor (IGF-1), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF); and cytokines such as transforming growth factor beta 1 (TGFβ 1), interleukin 1 alpha (IL-1α), and tumor necrosis factor alpha (TNF α). The signaling that follows at the border of dermal papillae and hair follicle in balding humans results in premature completion of anagen associated with premature entry into catagen. Catagen results from decreased expression of anagen maintenance factors such as the growth factors - IGF-1, bFGF and VEGF. In addition, increased expression of cytokines (TGFβ 1, IL -1α and TNF α) promotes apoptosis [5]. The Wnt/β catenin signaling pathway plays a leading role in hair regeneration and

supports the inductive properties of the dermal hair papilla. Androgens and ligand-activated AR negatively affect the Wnt/β catenin signaling pathway and also increase the expression of glycogen synthase kinase (GSK 3β) [5]

To date, it has been proven by scientists that the hair cycle is mostly regulated endogenously within the follicle itself and by the tissues of the immediate surroundings. During the entire hair cycle, the repetitive process of regression and regeneration can be seen only in the lower part of the follicle, which includes the suprabulbar and bulbar regions. At the same time, the upper part of the follicle, consisting of the isthmus and funnel, is a relatively stable structure [5].

Recent studies have shown that there are a large number of signaling molecules involved in the regulation of the hair cycle and hair follicle regeneration. These are certain genes, some families of growth factors, nuclear receptors, cytokines, and intracellular signaling pathways [6]. Each stage of follicle morphological development is characterized by a unique pattern of expression of growth factors, their receptors and antagonists, adhesion molecules and components of intracellular signaling [6]. But special attention should be paid to growth factors - tissue-specific cytokines of local action, which can exert their action in endocrine, paracrine and autocrine ways and enhance regeneration of hair follicle cells [7].

Purpose of the study: improvement of the pathogenetic method of androgenic alopecia treatment with the use of growth factors of plant origin.

## 2. MATERIALS AND METHODS

We observed 110 patients with androgenic alopecia, aged from 18 years to 58 years, among whom 58 were females and 52 were males. In 18 (34.61%) men there was I-II androgenic alopecia according to Hamilton, in which clinically there was hair loss only in the frontal region of the scalp; in 14 (26. 92%) men - III degree, in which hair loss in the forehead and temples was clinically noted; 20 (38,46%) men had IV -V degree of androgenic alopecia, in which there were pronounced bald spots in the frontal-parietal region of the scalp, formed by the fusion of areas of hair loss. The majority of women had Ludwig grade I 36 (62.06%), in which a small (0.7-1 cm wide) thinning of hair in the parietal region of the scalp was observed. In 22 (37.9%) female patients, II-III degree of the disease was noted, which was clinically characterized by significant hair thinning in the frontoparietal region of the scalp. The provoking factor in patients with androgenic alopecia were: - stressful conditions 29,4%, smoking - 16,7%, SARS 19 - 37,5%, diseases of ENT organs - 16,4%.

All patients with androgenic alopecia were subjected to videotrichodermatoscopic examination of the scalp using Aramo-SG video camera (Korea) with X60 and X200 lenses and Trichoscience diagnostic program. This scalp skin diagnostics is necessary not only for accurate diagnosis, but also for determining the effectiveness of therapy and its monitoring. One of the important criteria of videotrichodermatoscopic examination of scalp skin in androgenic alopecia is phototrichogram, which showed the presence of vellus-like hair from 43% to 65%. Hormonal status (LH, FSH, DHS, SSH, 17-OH) was also determined in female patients with androgenic hair loss. These hormone levels in female patients with androgenic alopecia were higher than normal in 16.3% of cases and the patients were referred for endocrinologist consultation. In males, free testosterone was examined, which was high in 4% of cases.

In all patients with androgenic alopecia were investigated stem cell markers before treatment and after the therapy - CD117, CD34, HGF and E2 (PGE2) in blood by automated immunoenzymatic method on the device “Humareader Single”. The results of the assays were counted spectrophotometrically at a wavelength of 450 nm. Measurements were performed immediately after stopping the reaction.

Results and Discussion. All patients were divided into 2 groups for the purpose of therapy: Group 1 (39 people) - patients who received traditional therapy according to the “Standards of Diagnosis and Treatment” (angioprotectors, herbal preparations with dwarf palm extract, vitamin therapy and platelet-rich plasma mesotherapeutically); Group 2 (42 people) - patients who received mesotherapeutically plant growth factors “Vitten Hair RX” (Cellcurin; PnP Biopharm, Seoul, Korea) into the scalp against the background of traditional therapy. This preparation consists of growth factors, plant extracts with anti-androgenic activity: basic fibroblast growth factor (FGF, 2.5 µg/mL), vascular endothelial growth factor (VEFG, 2.5 µg/mL), keratinocyte growth factor-2 (KGF-2, 2.5 µg/mL), stem cell factor (SCF, 2.5 µg/mL), insulin-like growth factor-1 (IGF-1, 1.25 µg/mL), fibroblast growth factor 9 (FGF9, 2.5 µg/mL), superoxide dismutase-1 (SOD-1.5 µg/mL) and noggin peptide (10 µg/mL), Thuja occidentalis leaf extract, Polygonum Multiflorum root extract, Oryza Sativa extract, Panax ginseng root extract, Camellia sinensis leaf extract, Vitis Vinifera grape seed extract, Licorice. This preparation was injected in the amount of 2.5 ml (the dry mixture was diluted with isotonic sodium chloride solution) intradermally on the scalp at a depth of 0.5 mm every 2 weeks for 3 months.

The study of differential markers of stem cells CD117, CD34 in the blood of patients with androgenic alopecia showed their reliable increase both after traditional therapy and after pathogenetic therapy with the inclusion of plant growth factors mesotherapeutically. Thus, the marker CD34 during traditional therapy significantly increased and amounted to - 5,94±1,6 ng/ml ($p<0,001$), and during pathogenetic therapy even more significantly increased in 6 times and amounted to 8,04±1,9 ng/ml ($p<0,001$) relative to the similar index in the group before treatment 1,26±1,3 ng/ml (Table 1). Marker CD117 during traditional therapy significantly increased and amounted to 15,7±2,8 ng/ml ($p<0,001$), and during pathogenetic therapy this marker significantly increased 7 times and amounted to 21,6±3,12 ng/ml ($p<0,001$) relative to the similar index in the group

before treatment 2,9±0,3 ng/ml.

**Table 1. Stem cell markers in patients with androgenic alopecia following treatment therapy**

| Stem cell markers (ng/ml) | | | Androgenic alopecia patients | |
|---|---|---|---|---|
| | control group (n=20) | Before treatment (n=53) | conventional therapy (n=39) | Traditional therapy + mesotherapy “Vitten Hair RX” (n=42) |
| CD34 | 10,2±2,8 | 1,26±1,3 | 5,94±1,6*** | 8,04±1,9*** |
| CD117 | 25,4±5,1 | 2,9±0,3 | 15,7±2,8*** | 21,6±3,12*** |

Note: * - differences with respect to the data of the control group are significant

The study of hepatocyte growth factor (HGF) in patients with androgenic alopecia after traditional and pathogenetic therapy showed a significant increase — 403.1±23.6 ng/ml ($p<0.001$) and 619.2±41.8 ng/ml ($p<0.001$), respectively — compared to the baseline level in patients before treatment, which was 293.87±32.3 ng/ml (Table 2).

As for prostaglandin E2 in patients with androgenic alopecia, its blood concentration showed a significant decrease in both therapy groups: in the traditional therapy group — 154.3±19.8 ng/ml ($p<0.001$), and in the pathogenetic therapy group — 108.1±17.6 ng/ml ($p<0.001$), whereas the baseline level in patients with androgenic alopecia before treatment was 371.6±25.7 ng/ml.

It should be noted that the levels of hepatocyte growth factor (HGF), prostaglandin E2, and stem cell markers CD34 and CD117 in patients with androgenic alopecia who received pathogenetic therapy including mesotherapeutic plant-derived growth factors reached levels similar to those of the control group.

**Table 2. Hepatocyte Growth Factor (HGF) and Prostaglandin E2 (PGE2) in Patients with Androgenic Alopecia After Therapy**

| Growth factors (ng/ml) | | | Пациенты андрогенной алопецией | |
|---|---|---|---|---|
| | control group (n=20) | до лечения (n=53) | control group (n=20) | Традиционная терапия + мезотерапия «Vitten Hair RX» (n=42) |
| HGF | 774,2±51,2 | 293,87±32,3 | 403,1±23,6** | 619,2±41,8*** |
| PGE2 | 98,56±4,5 | 371,6±25,7 | 154,3±19,8*** | 108,1±17,6*** |

Note: * - differences with respect to the data of the control group are significant

The results of the therapy are clinically presented in Table 3.

The most favorable hair growth outcomes were observed in Group 2 of patients with androgenic alopecia who received mesotherapeutic "Vitten Hair RX" in addition to traditional therapy. Specifically, vellus hair growth was noted on day 15.4±1.26 ($p<0.01$), terminal hair growth on day 19.1±2.01 ($p<0.01$), a reduction in hair loss by day 13.8±1.17 ($p<0.01$), and an increase in hair shaft diameter by 6.4%.

In contrast, Group 1 patients who received only traditional therapy demonstrated vellus hair growth on day 26.7±0.14, terminal hair growth on day 39.6±1.8, a reduction in hair loss by day 20.5±0.2, and an increase in hair shaft diameter by only 1.2%.

**Table 3. Results of Therapy in Patients with Androgenic Alopecia**

| Symptoms | Group 1 of patients receiving traditional therapy (days) | Group 2 of patients receiving pathogenetic therapy (days) |
|---|---|---|
| | (n=39) | (n=42) |
| Reduction in the number of shed hairs | 20,5±0,2 | 13,8±1,17** |
| Growth of vellus hairs | 26,7±0,14 | 15,4±1,26<br>*** |
| Growth of terminal hairs | 39,6±1,8 | 19,1±2,01<br>*** |
| Thickening of hair shafts | to 1,2%<br>- | to 6,4% |

Note: * - differences with respect to the data of the control group are significant

The positive dynamics of the studied growth factors, stem cell markers, and prostaglandin in patients with androgenic alopecia after pathogenetic therapy with the inclusion of plant-derived growth factors in mesotherapy demonstrates its determining role in the regeneration of the hair follicle. In addition to these growth factors enhancing the proliferation and mitosis of hair follicle cells, thus ensuring their transition into the anagen phase, they and the Noggin peptide also affect the signaling pathways of stem cell regeneration in the Bulge area—specifically the Wnt and BMP4 pathways.

Thus, FGF-9 is a growth factor that enhances hair follicle regeneration by activating the Wnt signaling pathway, which is essential for the development of hair follicles. FGF-5s inhibit FGF-5, thereby prolonging the hair growth cycle and increasing hair growth rate. The Noggin peptide inhibits the BMP4 stem cell signaling pathway, leading to the activation of WNTs and differentiation of hair follicle stem cells, which increases their proliferation.

## 3. CONCLUSIONS

Thus, treatment with plant-derived growth factors through mesotherapy in patients with androgenic alopecia demonstrates its high regenerative potential and influence on the hair follicle cycle. This not only strengthens and prolongs the anagen phase of the hair follicle but also increases hair diameter by five times.

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