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REVIEW ARTICLE

Plants as potential active components in treatment of androgenetic alopecia

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Summary

Androgenetic alopecia is caused by the influence of sex hormones on hair follicles and by hereditary factors. Characteristic for that type of alopecia is shortening of the hair growth phase and elongation of the rest phase caused by disturbance of the process of transformation of testosterone into dihydrotestosterone. Treatment of that type of alopecia involves 5α-reductase inhibitors, antagonists of the androgenic receptor or stimulating proliferation of cells to induce the hair growth. A number of plant raw materials work that way, thus they can be used in treatment of this type of alopecia.

Key words: *androgenetic alopecia, plant raw materials, topical treatment*

INTRODUCTION

Each day the hair falls out of head, especially during washing and combing. 70–100 hair loss a day is normal, however, losing over 100 hairs a day lasting longer than a few weeks indicates a serious problem. When more hair falls out than grows, hairstyle becomes thinner; if that process persists, even baldness may occur [1]. Alopecia can be of permanent or temporary type; it can cover various range and areas of haired head skin of various shapes. It occurs from numerous causes and the precise identification is rarely possible. Androgenetic alopecia and alopecia in course of haired head skin diseases that lead to scarification are of constant character [2, 3].

Androgenetic alopecia (*Alopecia androgenetica*) is a common phenomenon among most of men older than 40, but it also appears in women. The frequency increases with age, but it also depends on the race – Caucasians are more susceptible. Androgenetic alopecia is caused by the influence of hormones on hair follicles and by hereditary factors. Occurrence of such a type of alopecia is related to shortening of the hair growth phase (anagen) and elongation of the rest phase (telogen). Thus, it is so-called telogen alopecia (*effluvium telogenicum*) which is characterised by precocious entering of the hair follicles into the involution (catagen) phase which proceeds correctly. After its completion, the percentage of telogen hair increases abnormally. Then, miniaturization of hair follicles and increased hair falling occurs. Single hairs are replaced with new, but much thinner, which are soon replaced with down becoming almost imperceptible and easily lost [2, 4, 5]. Those changes are caused by the disturbance of conversion of the testosterone (T) into dihydrotestosterone (DHT). In general, increased secretion of hormones in men has not been discovered, but they show higher vulnerability of hair follicles to androgens in some areas of the head skin [3, 4].

Testosterone is being reduced to DHT by 5α-reductase (5αR) with help of reduced NADPH cofactor. In the human organism, two forms of 5αR occur: 5αR type I and 5αR type II. It has been shown that 5αR type II can be found in head skin and it significantly affects hair growth. DHT stimulates hair follicles on the face and genital organs area but slows down hair growing on the haired head skin. It merges with the androgen receptor, forming the androgen-androgen receptor complex. That complex undergoes enzymatic transformations which activate it. This activation enables its binding to specific locations in active genes located in hair papilla cells and induces the secretion of cytokines triggering transformation of hair follicles into miniaturized follicles [2, 4].

Androgen receptors are unevenly spaced in follicles of head skin, which results in characteristic male alopecia pattern – initially in the forehead-temple area and next on the top of head. Subsequently, only the circle around the head remains haired [3].

Due to the mechanism of androgenetic alopecia described above, treatment with inhibitors which slow down the reduction of testosterone into DHT or androgen receptor's antagonists, binding with the androgen receptor in the hair follicle is possible. The third method of treatment is induction of cell proliferation in order to accelerate hair growth [4].

There are many plant raw materials which are believed to be hair growth inducing or preventing from alopecia. Often it is not perfectly clear how they do work. It is suggested that they accelerate blood circulation in skin capillaries which improves the nutrition of hair follicles. Some of them also inhibit the conversion of testosterone into dihydrotestosterone, thus they are recommended in the therapy of androgenetic alopecia [6, 7]. Results of investigation of the influence of herbal extracts on androgenetic alopecia process are hereafter presented. In future, herbal extracts displaying positive activity may serve as ingredients of cosmetic and therapeutic preparates successfully used in the treatment of this affliction [4].

PLANT RAW MATERIALS

Extract from the seeds of thuya (*Thuja occidentalis*) appeared to be an inhibitor of 5αR type II *in vitro*, whereas *in vivo* 1% extract from this plant, applied locally in mice with androgenetic alopecia, resulted in the setback of alopecia. Ingredients responsible for that property were diterpenes and flavonoids, inhibiting 5αR [4, 8].

Extract from dried roots of Ku Shen (*Sophora flavescens*) applied locally on the mice skin caused rapid transmission of hair follicles from the telogen phase into anagen one. Analysis of the culture of human dermal papilla cells showed the increased level of mRNA of growth factors IGF-1 and KGF. Moreover, it has been found that extract from *Sophora flavescens* roots strongly inhibits the influence of 5αR type II, probably due to the content of,among others, prenylflavonoids, prenylflavones and pterocarpans [4, 9].

Other study focused on antiandrogenic activity of extracts from various Japanese plants. The analysis concerned 50% ethanol extract from the bark of Myrica (*Myrica rubra*) and 50% ethanol extract from the blossom of Ramanas rose (Japanese rose) – *Rosa rugosa* (*Rosaceae*). The *in vitro* test showed stronger inhibition of the 5αR by the *Myricae cortex* extract as compared to the extract from *Rosae rugosae flos* used in Japanese cosmetics stimulating hair growth. Two *in vivo* tests of androgenic activity carried out on mice, in which hair growth on the shaved skin was observed, suggested that activity of Myrica bark extract is higher than that of the extract from the Ramanas rose [10].

Among active compounds present in the Myrica bark in *in vitro* test, myricanon and myricanol showed similar properties of inhibiting 5α-reductase, myricetine's activity was weaker and myricitrin did not show such activity at all.

In *in vivo* tests of androgenic activity, myricanol, myricetin and also myricitrin displayed positive effect on hair growth. The last of those compounds, which *in vitro* is not an inhibitor of 5αR, probably acts by inhibiting the bonding between DHT and androgenic receptor in hair follicles and/or inhibiting the protein synthesis [10].

The study also covered *in vitro* inhibition of 5αR by 50% ethanol extracts from several different parts of six species of *Piper* in concentrations of 1 and 2 mg/ml: *Piper nigrum, P. methysticum, P. betle, P. katsura, P. longum* and *P. cubeba*. Amongst them, extracts from leaves and fruit of *P. nigrum* and fruit of *P. cubeba* revealed strong inhibiting activity in the concentration of 2 mg/ml [11].

Active compounds responsible for the inhibition of 5αR were (–)-cubebin and (–)-3,4-dimethoxy-3,4-desmethylenodioxycubebin from *P. nigrum* leaves, (–)-cubebin present in *P. cubeba* fruit and piperine, main alkaloid derivative from *P. nigrum* fruit. Such properties of (–)-cubebene and piperine were revealed for the first time in that study. Moreover, 5% solution of methanol extract from *P. Nigrum* leaves, applied locally during the *in vivo* test of hair growth in mice responsive to testosterone, revealed strong antiandrogenic properties [11].

Liposterolic extract from the fruit of Saw Palmetto – *Serenoa repens* (*Sabal serrulata*) – is an inhibitor of 5α-reductase, used in treatment of benign prostatic

hyperplasia. It also hampers binding of DHT to androgenic receptors. The raw material contains phytosterols: β-sitosterol, campesterol, stigmasterol and unsaturated fatty acids which are responsible for its activity. It is suggested to use the saw palmetto extract in treatment of the first condition, due to similar mechanisms of the onset of androgenetic alopecia and benign prostatic hyperplasia and positive results of the two studies carried out, even though in a small group of patients. In the study involving 10 men aged 23–64, suffering from androgenetic alopecia, an improvement of 60% has been observed after oral administration. In another experiment, 34 men and 28 women, aged 18–48, were applying locally emulsion and shampoo with extract from saw palmetto for three months. A 35% increase of hair density and 67% reduction of sebum were proved [4, 12, 13].

Rho et al. studied 45 herbal extracts from plants traditionally used by oriental medicine in treatment of hair loss aiming at identifying potential hair growth promoters. Extract from *Asiasari radix* (extract from roots and/or rhizomes of *Asiasarum heterotropoides* var. *mandshuricum* or *Asiasarum sieboldi*) appeared to have the strongest stimulating effect on hair growth in mice. When applied locally, it caused transition of the hair follicle from the telogen to the anagen phase and stimulated proliferation of cells in the follicle, which was confirmed by histological examination. Experiments carried out on cultures of hair papillae, isolated from head skin of men aged 25–30, showed that extract from *Asiasari radix* increased the expression of the Vascular Endothelial Growth Factor (VEGF) and thus stimulated the hair growth. Major active compounds of that extract were methyleugenol, dneol, saflore and 1-asarine. That study did not show any inhibiting impact of *Asiasari radix* extract on 5α-reductase. However, on the basis of its ability to stimulate proliferation of hair follicle cells and increasing expression of VEGF, it seems to be a good candidate to be a stimulant of hair growth also in androgenetic alopecia [4, 14].

Similar properties can be observed for water-soluble extract from leaves, fruit and roots of Japanese star anise (shikimi) – *Illicium anisatum*. It has been observed that it increases the blood flow in the subcutaneous layer in animal model. In mice, i*n vitro* study of hair follicles resulted in the increased hair growth after local application of that extract. The main active substance of the abovementioned extract is shikimic acid. For the determination of the mechanism conditioning the hair growth, the expression level of mRNA of such growth factors as IGF-1, VEGF, KGF and HGF/SF in hair follicles of mice after 1, 2, 3, 4 and 7 days was studied. A significant increase of expression of mRNA growth factors IGF-1 and VEGF at the early stage, more gradual increase of the expression of mRNA growth factor KGF and no influence on expression of mRNA HGF/SF were observed. Presented results show that shikimic acid from water-soluble extract from *Illicium anisatum* may have positive influence on hair growth, by adjusting the level of IGF-1, VEGF and KGF in hair follicles [15].

Another plant showing the property of inducing transition of hair follicles from telogen into anagen is *Eclipta alba*. *In vivo* study on mice, with local application of methanol extract from that plant, confirmed its ability to promote hair growth,

the strongest for the dose of 3.2 mg/15 cm^2. Phytochemical analyses displayed that methanol extract contained coumestans, triterpenoid glycosides, thiophene derivatives, triterpenoid saponins, flavonoids and wedelolactone. Details of the mechanism of *Eclipta alba*'s activity are still under study [16].

Extracts from leaves and flowers of Hibiscus – *Hibiscus rosa-sinensis* – were applied locally for 30 days on shaved skin of albino rats, in the form of 1-percent extracts in liquid paraffin. After 15 days, in all groups, beginning of hair growth and its continuation until the end of the experiment was observed. Extract from leaves showed greater influence on hair length than extract from flowers. After 30 days, 17 mm of hair growth in animals subjected to the activity of leaf extract, compared to 15, 8 mm of hair growth in the group subjected to the activity of flower extract was obtained. For the placebo and control groups, respective values were 14,5 mm and 13,6 mm. Presented results may confirm properties of the extract from Hibiscus leaves stimulating transition of hair follicles from the telogen to the anagen phase. At the end of the study, it was observed that 67% of all hair follicles stimulated by that extract were in the anagen phase. The amount of anagen hair follicles in the flower extract testing group was 60%, in the *placebo* group – 54% and in the control group – 50%. *In vitro* study on hair follicles gained from mice newborns confirmed that observation. After 72 hours, extract from the leaves of *Hibiscus rosa-sinensis* caused the greatest growth of the hair follicles. Thus, it can be taken into consideration as a hair growth cosmetic preparations' ingredient [17].

The extract from the root of Ginseng (*Panax ginseng*) is an ingredient of some shampoos and hair conditioners. 70% methanol extracts from the raw materials called "white ginseng" and "red ginseng" and saponins isolated from them were studied with special consideration of their influence on hair growth in the *in vitro* culture of hair follicle cells in mice. "White ginseng" is the root subjected to the action of sulphur dioxide and sun-dried or dried at a temperature of 100–200°C, whereas „red ginseng" is obtained after sterilisation with water vapour at a temperature of 120–130°C for 2–3 hours [18]. It was observed that the extract from the „red ginseng" root promoted hair growth, depending on the dose, after both 48 hours and 72 hours of culture. The dose of 50 μg/ml had the greatest influence. The action of white ginseng root extract was significantly weaker. Those results suggest that large amounts of ginsenosides present in red ginseng play a significant role in stimulating hair growth [18].

Until now, 26 triterpene saponins in *Ginseng radix* have been isolated and identified. They are combinations of panaxadiol aglycones (e.g. ginsenosides Rb_1, Rb_2), panaxatriol (e.g. ginsenosides Rg_1, Rg_2) and oleanolic acid (ginsenoside R_0) with particles of monosaccharides. In order to discover which of the compounds promotes hair growth, 3 ginsenosides were studied: Rb_1, Rg_1 and R_0. It appeared that ginsenoside Rb_1 promoted hair growth depending on the dose, with most significant effect at 10 μg/ml after 48 hours of culture. Thus, it can condition properties activating hair growth in red ginseng, as it is present there in a relatively high amount [18]. Also ginsenosides R_0 and Rg_2 enhance *in vivo*

hair re-growth based on their inhibitory activity against 5αR in the androgenetic alopecia model [19].

Promising drugs for treating androgenetic alopecia are extracts of *Puerariae Flos*, *Ecklonia cava* and *Ishige sinicola*. The 50% ethanolic extract of *Puerariae Flos* (the flowers of *Pueraria thomsonii*) showed inhibitory activity of 60.2% at 500 μg/ml against testosterone 5α-reductase and it was more potent than that of *Puerariae radix* (roots of *Pueraria lobata*) [20]. *E. cava* enzymatic extract, dieckol from *E. cava*, *I. sinicola* extract and octaphlorethol A, a principal of *I. sinicola* can stimulate hair growth by the proliferation of DPC (dermal papilla cells) and the inhibition of 5α-reductase activity [21, 22].

Rosmarinus officinalis leaf extract promotes hair growth by accelerating blood circulation in skin capillaries, which improves nutrition of hair follicles [23]. Topical administration of *R. officinalis* leaf extract also showed inhibitory activity of 82.4% and 94.6% at 200 and 500 μg/mL, respectively, against 5αR [24].

CONCLUSIONS

Results of the study on the influence of herbal extracts on hair growth carried out in recent years are promising. The raw materials described may be effective in the treatment of androgenetic alopecia and some of them also in treatment of other types of baldness. Therefore, for the confirmation of the results obtained during experiments carried out on animals, *in vitro* and *in vivo*, clinical studies are required. They will constitute the basis for application of the above described herbal extracts in cosmetic preparations and in drugs hampering hair loss.

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SUROWCE ROŚLINNE JAKO POTENCJALNE SKŁADNIKI AKTYWNE W TERAPII ŁYSIENIA ANDROGENOWEGO

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Streszczenie

Łysienie androgenowe spowodowane jest wpływem hormonów płciowych na mieszki włosowe oraz czynnikami dziedzicznymi. W przebiegu tego typu łysienia charakterystyczne jest skrócenie fazy wzrostu włosa i wydłużenie fazy spoczynku, spowodowane zaburzeniem procesu przekształcania testosteronu w dihydrotestosteron. W terapii tego typu łysienia stosuje się inhibitory 5α-reduktazy, antagonistów receptora androgenowego lub stymuluje proliferację komórek, w celu przyśpieszenia wzrostu włosa. Wiele surowców roślinnych działa według powyższych mechanizmów, dlatego mogą być wykorzystane w terapii tego typu łysienia.

Słowa kluczowe: *łysienie androgenowe, surowce roślinne, leczenie miejscowe*