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Selected Synthetic and Natural Actives as Inhibitors in Androgenic Alopecia

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Summary

Androgenic alopecia is a common condition that affects Caucasian males in the age range between 20 and 40. A paper discusses briefly pathogenesis of androgenic hair loss in men and the factors affecting its development.

The main part of the paper describes selected actives inhibiting androgenic alopecia and their mechanism of action, recalling the results of their effectiveness testing in vivo. It discusses the widely used active substances such as finasteride and minoxidil and a range of plant materials used in traditional medicine for potential use in practice. Unfortunately, not for all interesting plants are available results of human efficacy studies.

Riassunto

La alopecia androgenetica è una comune affezione che colpisce la razza caucasica soprattutto di sesso maschile e di età compresa tra 20 e 40 anni. Il lavoro descrive brevemente la patogenesi e lo sviluppo di questa patologia nell'uomo. La parte principale dello studio riporta i più importanti ingredienti attivi utilizzati per inibire lo sviluppo della alopecia androgenetica, descrivendone anche i meccanismi d'azione ed i risultati di efficacia condotti *in vivo*.

Tra gli attivi utilizzati viene discussa l'attività svolta dalla finasteride e dal minoxidil, oltre che da diversi estratti vegetali utilizzati dalla medicina tradizionale.

Sfortunatamente per molte piante medicinali non sono reperibili i risultati ottenuti *in vivo*.

INTRODUCTION

Androgenic alopecia is a common condition that affects males in the age range between 20 and 40, constituting a serious psychological problem. According to research findings, patients suffering from extensive androgenic hair loss have a worse quality of life. Psychic distress is comparable to that experienced in the course of such serious conditions as, e.g. psoriasis. For this reason, it is crucial to cooperate with a dermatologist who will help a patient to comprehend the factors underlying the development of this condition and will help to select an appropriate treatment. The therapy of androgenic alopecia is time-consuming and requires a lot of patience as well as regularity in taking medicines.

PATHOGENESIS OF ANDROGENIC HAIR LOSS IN MEN AND THE FACTORS AFFECTING ITS DEVELOPMENT

The etiology of androgenic alopecia is usually connected with the level of androgens, genetic susceptibility and age. The condition is inherited in an autosomal dominant or multigenic way. Multigenic inheritance is related to the occurrence of early balding in the family, a significant prevalence of the condition in the family and heterogeneity of its clinical manifestation. Premature androgenic hair loss is probably conditioned by an autosomal gene.

Probability for a male to be affected is dependent on the number of relatives suffering from androgenic hair loss of the 1st and 2nd degree. When balding of this type affects the patient's sister or mother, the prognosis is considerably worse (1). In individuals who have genetic predispositions, the androgen level may be correct and does not have to be a factor in the development of the condition. Over 50% males after 40 are affected by the hair loss which is indirectly rooted in androgen activity. In 1942 Hamilton discovered that androgenic hair loss is not present in eunuchs. It appeared when they were given testosterone. In 1974 a hereditary anomaly was discovered, a male pseudohermaphroditism[1].

It was a very important discovery in the context of searching a medicine for androgenic alopecia. Children born with pseudohermaphroditism possessed female phenotypic traits, external sex organs were not fully differentiated, yet until puberty, when male traits appeared, the children were treated as girls. As adults, they possessed thin hair, yet with no clinical balding symptoms, no acne, or the prostate did not enlarge.

Research showed that those individuals had a deficiency of the enzyme, type II 5-alpha-reductase, which affected the correct conversion of testosterone to DHT (2). Androgenic alopecia is not present in individuals who have a geneticall-ly conditioned deficiency of the type II 5-alpha-reductase. Since the fontanelle and forehead areas are formed from the neural crest and are characterized by a higher 5-alpha-reductase activity, a more profound hair loss occurs in these areas, whereas the occipital part develops from the mesoderm, and there the hair remains. This is connected with a different metabolism of testosterone by the hair follicle. Testosterone is transformed into 5-alpha-dihydrotestosterone (DHT) and only then does it function in target tissues [2,1].

5-alpha-dihydrotestosterone has a higher affinity for androgenic receptors, forming more stable complexes. The number of 5-alpha-dihydrotestosterone and testosterone receptors is dependent on the individual's age and head area. In the forehead they are more densely located than they are in the occipital part. The conversion of testosterone into DHT is controlled by two isoenzymes, 5-alpha-reductase type I and type II. In hair follicles 5-alpha-reductase type I is present only in sebaceous glands, whereas 5-alpha-reductase type II is present in the sebaceous duct, outer

root sheath and inner root sheath[1].

Selected actives inhibiting androgenic alopecia and their mechanism of action

Finasteride

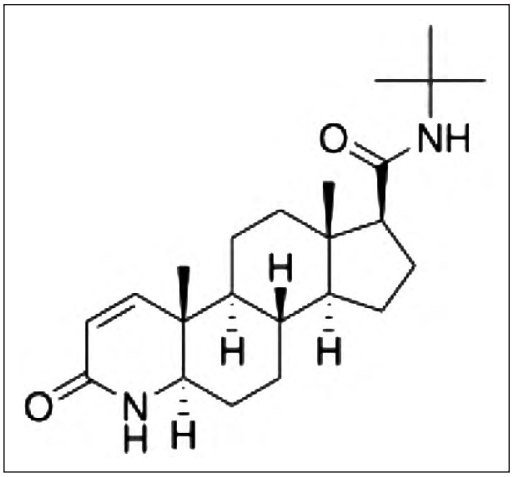

Fig. 1 *Finasteride.*

Finasteride is a synthetic 4-azasteroid compound. Most importantly, it is an inhibitor of type II 5-alpha-reducatse, which transforms testosterone into its active form, DHT, .i.e. 5-alpha-dihydrotestosterone(3,4). In rats, mice, apes and humans two isoenzymes (I and II type) have been discovered, with differing expression in the tissues. In humans, 5-alpha-reductase (type I) is present is liver and in sebaceous glands in the skin, whereas type II is present in such organs as: prostate, epididymides, seminal vesicles, and hair follicles (5). The mechanism of action of finasteride rests upon inhibiting the activity of isoenzyme type II. The conversion of testosterone into 5-alpha-dihydrotestosterone is blocked. The activity of finasteride has an impact on the inhibition of the key factor in the development of androgenic alopecia in individuals who are genetically susceptible. In the first year of treatment the number of hair follicles that react to the finasteride treatment is established. The further therapy aims to maintain the effects (6). Since 1992 finasteride has been administered orally in the 5 mg dose as a drug for prostatic hyperplasia. The drug containing finasteride, *Propecia*, is also used in androgenic alopecia in men (7).

Leyden et al. conducted a study in 15 locations in the United States. Randomly selected individuals were administered 1 mg oral dose of finasteride vs. placebo once daily for 12 months, and all participants took part in further research throughout the following year. The hair number was assessed in a blind study in the 6th, 12th and 24th month. The photographs of the frontal (anterior/mid) scalp in the 6th, 12th and 24th month, respectively, were evaluated by a team of dermatologists at the end of the treatment (8).

Finasteride proved to be efficacious in the treatment of men with head top hair loss. At present, research is devoted to the efficacy of the treatment in the frontal/mid scalp. Whereas the above treatment referred to the head top primarily, over a half of the subjects had a problem with hair loss in the frontal and mid part of the scalp. After the 12-month treatment the mean hair count per 1cm^2 scalp increased by 12 hairs. It was established that there is a correlation: the lower hair thickness at the onset of the therapy, the higher hair increase in response to finasteride. All methods used to evaluate the results revealed the supremacy of finasteride over placebo.

At first, finasteride slows down the miniaturisation of hair follicles and stimulates hair growth. In the following phases of the treatment hairs become longer and thicker. There have not been discovered any considerable adverse side effects of the treatment with finasteride (7).

TABLE I

Finasteride efficacy study results.

Finasteride action	Finasteride dosage applied	Results after 12 months' treatment
HAIR COUNT	1 mg/day	Hair count in the group treated with finasteride increased by 9.6 items/1cm^2 in comparison with the control group, where the hair number decreased by 2.0 items/ 1 cm^2.
ENHANCEMENT OF HAIR APPEARANCE	1 mg/day	In 37% patients treated with finasteride an improvement in hair appearance was noticed, as related to the control group with only 7% improvement.
HAIR LOSS INHIBITION	1 mg/day	70% patients treated with finasteride did not notice further hair loss, whereas 30% individuals noticed further hair loss.

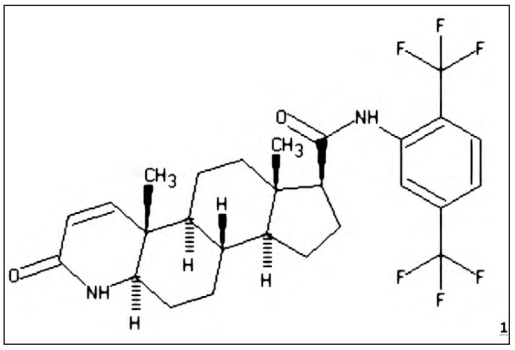

Fig. 2 *Dutasteride.*

Dutasteride is a powerful, selective oral inhibitor of 5-alpha-reductase type I and II in humans. It lowers the level of dihydrotestosterone in the blood serum(9). Stough et al. conducted a study on monozygotic twins in order to evaluate the impact of phenotypical and environmental factors on androgenic alopecia. Twins are a perfect object of study of the efficacy of a drug for hair loss whose expression is determined genetically. Twins possess the same genetic code and thus it is easy to determine the impact of both substances on the therapy when one of them is administered a drug and the second one a placebo (10). The main objective of the study was to determine the efficacy of dutasteride as a hair loss inhibitor. The secondary objective was to evaluate its impact on the hair count and hair appearance assessment (self-assessment). Throughout the study phenotype changes in genetically identical twins were being monitored[10].

In this study dutasteride considerably contributed to the improvement of hair growth throughout one year, and none of dutasteride-treated patients noticed the deterioration in hair growth, unlike patients in the placebo group.

Asarum europaeum

Asiasari radix serves as a natural herbal medicine used in China to treat oral cavity and gingiva inflammations. The plant is known for its analgesic and anti-inflammatory properties, as well

as its protective activity against brain cell damage. It also promotes hair growth (11). For the purposes of the research the root of *Asarum europaeum-Asiasari radix* was used. It proved to be efficacious in the telogen-to-anagen conversion of hair follicles. It was revealed that the *Asiasari radix* extract had contributed to cellular proliferation, protein synthesis and promoted cellular growth. From 45 plants used in oriental medicine, *Asiasari radix* proved to have the most hair growth-promoting potential. Seok-Seon Rho et al. conducted a 45-day experiment on mice that were topically treated with *Asiasari radix* extract on their shaven backs. The effects were additionally evaluated in vitro on keratinocytes and human dermal papilla cells (11).

TABLE II

Finasteride efficacy study results.

Dutasteride action	**Dosage applied**	**Results after 12 months**
Hair length growth	0,5 mg/day	Due to dutasteride activity hair length increased on average by 35 mm in comparison with the control group
Increased hair count	0,5 mg/day	In the treatment group the hair count i ncreased by approximately 16.5 hairs/1cm^2 in comparison with the control group, approximately 3.8 hairs/1cm^2 more.

TABLE III

Results of the research on the Asarum europaeum root extract.

Asiasari radix extract action	**Applied dosage (ethanol mixture)**	**Result**
CELLULAR PROLIFERATION	0.0001 %	Visible cellular proliferation growth reaching 115.6 % in comparison with the control object.
POTENTIAL TO UPTAKE CYSTEINE IN HAIR FOLLICLE	0.0001 %	Cysteine uptake in the hair follicle was increased by 129% in comparison with the control object.
TELOGEN-TO-ANAGEN CONVERSION OF HAIR FOLLICLES	0.0001%	The picture showing a histological examination of the skin sample clearly shows the evoked anagen phase, with hair follicles thicker and more deeply-set in comparison with the control object.

To sum up, the Asiasari radix extract proved to be effective in promoting hair growth. It also contributes to promoting the phase of a rapid hair growth, the anagen phase; cellular proliferation of the dermal papilla and to the increased ability to absorb cysteine in the hair follicle, which results in protein synthesis in the hair follicle. However, no impact on the activity of 5-alpha-reductase was discovered. Potentially, treating androgenic alopecia with this vegetable extract could be a valuable alternative to commonly used hair loss inhibitors, such as minoxidil, finasteride, or dutasteride. So far no research has been conducted on the hair loss inhibition of Asiasari radix on humans.

Zizyphus jujuba

Over one thousand plants have been studied recently to assess their impact on hair growth promotion. Despite the fact that vegetable extracts are not that commonly used in the treatment of androgenic alopecia, alternative medicine is becoming increasingly more popular. The plant that has proved to be effective as an androgenic hair loss inhibitor, is *Zizyphus jujuba*. *Zizyphus jujuba* is a plant widely distributed in Europe and Southeast Asia. It reveals medicinal properties, including analgesic and anti-diabetic. Indigeneous tribes used bark from this tree for birth control purposes (12).

The experiment was conducted on 5-week old mice with shaven backs so that *Zizyphus jujuba* seed essential oil could be applied topically. The treatment lasted for 7 days, and its efficacy was evaluated immediately after the therapy and after 14 and 21 days after the treatment. Ten randomly extracted hairs were examined with respect to their length, thickness and mass[12].

TABLE IV

Experiment results testifying to the efficacy of the essential oil from Ziziphus jujube seeds.

Zizyphus jujuba essential oil action	**Dosage applied**	**Results after 21 days**
HAIR LENGTH	1 μL	Hair growth increased on average up to 10.02 mm with reference to the control group; on average 8.94 mm.
HAIR THICKNESS	1 μL	Hair thickness increased up to approximately 4.8 mm in comparison with the control group, with 4.1 mm.
HAIR MASS	1 μL	Hair mass increased up to approximately 54 mg/cm^2 in comparison with the control group, with 50 mg/cm^2.

Summing up, essential oil from *Zizyphus jujuba* seeds has a beneficial effect on hair growth. After 21 days of experiment, hair count on the backs of the treated mice considerably outnumbered the hair count on the backs of the mice that had not been treated with this essential oil. Such a comparison makes it possible to verify that the number of hairs in the phase of the rapid hair growth, i.e., anagen, increased. Hair mass and thickness increased as well. Unfortunately, the exact mechanism of action has not been discovered yet; nevertheless, the experiment substantiates the statement that the oil used undoubtedly stimulates hair growth. So far this kind of study with the use of *Zizyphus jujuba* has not been conducted on humans.

Fallopia multiflora

Increasingly more studies are being conducted in order to evaluate the activity of traditional herbal medicines that prevent hair loss. One of the plants from this group is *Fallopia multiflora*, known as Fo-Ti and *Polygonum multiflorum*. It is commonly used in Eastern Asia in patients suffering from hair loss and as lipid plasma level lowering food supplement (13). Hye-Jin Park et al. decided to conduct research on the impact of *Fallopia multiflora* on hair growth[14].

Study findings confirmed the efficacy of fallopia extract in promoting hair growth. In the group treated with the vegetable extract a considerable increase in the hair length occurred in comparison with the control group. The plant had contributed to the increase in hair length. The experiment proved that the intense hair growth phase was triggered through the activation of beta-catenin, which plays a crucial role in regulating hair follicle growth. Before, experiments concerning the action of *Fallopia multiflora* on humans had not been conducted.

TABLE V

Results confirming the efficacy of Fallopia multiflora extract.

Fallopia multiflora action objective	**Extract concentration used**	**Results after 4 weeks of application**
NUMBER OF HAIR FOLLICLES	4.7 mg/ 12 cm^2	In every following week the number of hair follicles increased. After 4 weeks of application the average number of follicles was 15, in comparison with the control group, with 11 follicles on average.
HAIR LENGTH	4.7 mg/ 12 cm^2	In every following week hair length increased. After 4 weeks it was 65 mm on average in comparison with the control group, with the average 55 mm.

Minoxidil

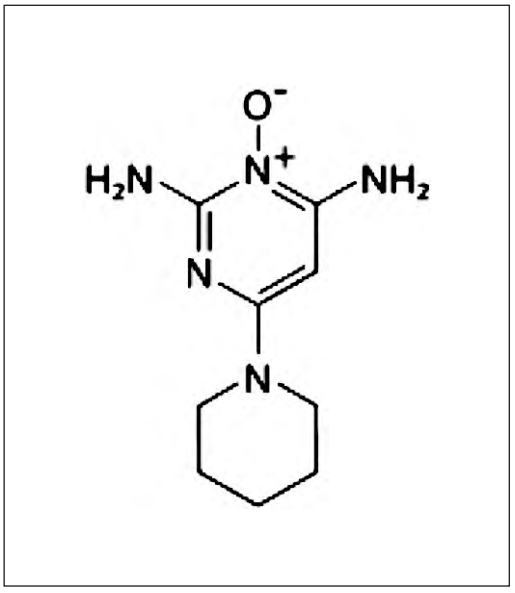

Fig. 3 *Minoxidil.*

Minoxidil is a 2,4-diaminopyrimidine derivative. It was introduced to therapeutics in 1970 as an oral drug for severe hypertension in the cases of resistance to other medications. During minoxidil therapy there appeared a side effect, namely excessive hair growth. The phenomenon raised interest and this led to the decision to use this substance in androgenic alopecia treatment. Since 1986 minoxidil has been classified as a substance promoting hair regrowth[1]. Despite over 20 years of research still the knowledge of precise mechanisms of action of minoxidil on hair growth is limited. There are numerous possible explanations for the influence of the medicine on hair, e.g., by promoting its growth rate; shortening the telogen phase, while prolonging the intense growth phase, i.e., anagen; or by increasing hair thickness and length[15].

Mi Hee Kwack et al. decided to undertake research in order to assess how minoxidil affects hair. The recent experiments on mice have revealed that beta-catenin is active in anagen hair, whereas when a premature catagen phase occurs, its activity is inhibited. The findings indicate that due to the presence of beta-catenin the intense hair growth phase may be prolonged. A topical treatment with minoxidil promotes hair growth in the androgenic hair loss of the male type, which suggests that it can have an impact on the prolongation of the anagen phase. The study was conducted on a hairy scalp sample, obtained from men suffering from androgenic alopecia in order to isolate hair follicles needed for the experiment. In order to evaluate if minoxidil initiates the anagen phase, an in vivo study was performed on 7-week old mice. Mice's backs were shaven and the hair growth was synchronized to the telogen. The therapy with 3% minoxidil lasted for 10 days. A profound delay in the catagen phase and the accumulation of beta-catenin in hairs were observed (15).

The mechanism of action of minoxidil rests upon its impact on the hair growth cycle; it shortens the resting phase, and at the same time it prolongs the hair's intense growth phase. This occurs as a result of the activation of beta-catenin in the hair follicle. Minoxidil turned out to be efficacious in promoting hair growth. Due to that, it can be used to treat androgenic alopecia.

Aminexil and SP94

Aminexil and SP 94 are actives present in L'Oreal market products recommended for hair loss. According to the manufacturer's claim, the products simultaneously strengthen the hair shaft and increase the number of hairs. Aminexil is 2,4-diaminopyrimidine 3-N-oxide.

SP94 is 6-O-linoleyl-D-glucose, which can take part in ceramide synthesis and provide structural ingredients for a strong, structurally homogeneous and thick hair shaft. L'Oreal experts conducted a study on Aminexil efficacy in a single blind trial. The study lasted for 3-6 months[16].

Chromatography analysis revealed that the product's mechanism of action rests primarily upon the transformation of a SP94 molecule into lipids (including ceramides - EOS and NS), which are responsible for the cohesiveness of the molecules that build the hair follicle and prevent hair sheath fibrosis [16].

Independent clinical trials with the use of products containing a mixture of Aminexil and SP 94 were conducted on a group of 180 people by Camacho et al. findings obtained in the trial confirm the inhibition of hair loss; however, the regrowth of lost hair was not confirmed 17. The actives present in the preparation may constitute an addition to the everyday hair care regime for the hair with the symptoms of androgenic alopecia.

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CONCLUSION

The progress of androgenic hair loss can be stopped primarily through 5-alpha-reductase inhibitors. There are pharmacological preparations available on the market. They are formulated for topical use and promote the improvement of hair condition in the case of male pattern androgenic hair loss. A therapy with the use of such substances as finasteride dutasteride, and minoxidil is time-consuming and requires regularity in its application. The interest of scientists in traditional, natural methods of preventing hair loss, including herbal medicines, is increasing. Herbal preparations based on vegetable extracts from the plants, such as Fallopia multiflora, *Asarum europaeum* and Zizyphus jujube may constitute a perfect alternative to pharmacological preparations, considering the risk of adverse side effects associated with taking the latter. There are also typically cosmetic methods to limit hair loss in balding, e.g., using preparations containing 2,4-diaminopirymidine-3-N-oxide.

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