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Efficacy of a Nutritional Supplement, Standardized in Fatty Acids and Phytosterols, on Hair Loss and Hair Health in both Women and Men

Federica Zanzottera[1*], **Gioia Bizzaro**[2], **Angela Michelotti** [2] **and Vincenzo Nobile** [2]

[1]*Private Practice Trichology, Milano, Italy*

[2]*Complife Group, Garbagnate Milanese, Italy*

[*]**Corresponding author:** Federica Zanzottera, Private Practice Trichology, Milano, Italy, Tel: +393482441779; E-mail: federica.zanzottera@hotmail.it

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Abstract

Introduction: Hair health concern is one of the most distressing conditions for a significant number of men and women of all ages. The unique current pharmacologic therapeutic options approved by Food and Drug administration (FDA) are finasteride and topical minoxidil; however, these treatments may have side effects and may work on just one cause of hair loss, without giving an exhaustive and complete results.

Objective: The aim of this study was to evaluate the efficacy of a nutritional complex, combining omega 3-6-9, antioxidant, natural inhibitors of 5α-reductase and anti-inflammatory molecules in improving hair loss and hair health parameter such as volume, strength and reduction of greasiness.

Methods: This study was made up of two phases. The in vitro experiment aimed at evaluating the capacity of the nutritional complex to lower the enzyme 5α-reductase activity in culture of human keratinocytes. The *in vivo* study was performed on 30 volunteers who experienced a 6 months treatment with the nutritional complex. The evaluation of hair loss and hair health parameter was performed by trichoscopy, global photograph review and subject's assessment.

Results: The *in vitro* study showed the capacity of the nutritional formulation to inhibit the total 5α-reductase comparable to finasteride and *Serenoa repens*. The global photograph assessment at T_0 and T_6 showed an increased hair density on 83.3% of subjects and the preliminary results were already visible just after three months. Moreover, the trichoscopy demonstrates an increase of hair diameter and hair density, an improvement of vascularization and a reduction of greasiness at the follicle level. The hair quality and hair loss reduction valued by the subjects showed positive results confirming the photographic outcomes.

Conclusions: This study proves the action of nutritional complex components, ß-sitosterosl with omega 3-6 complex from *Serenoa repens*, linseed, borage, wheat oils, pine bark and rye grass in inhibition of the total 5α-reductase. Furthermore, both the reduction of hair greasiness and the improvement of hair quality demonstrate that this formulation is not only effective against 5α-reductase but it also exerts its properties in a complete manner by restoring the physiologic condition of a healthy scalp. Moreover, it demonstrates the positive effects of this natural complex supplementation on overall scalp coverage. Visibly there is an improvement of vascularization, hair diameter and the reduction of hair loss perception.

Keywords: Androgenetic alopecia; Nutritional supplement; Hair loss; Hair growth; Female pattern hair loss; Omega 3 and 6; Antioxidants

Introduction

In the modern society, hair loss and hair health concern are one of the most distressing condition for a significant number of men and women of all ages.

Among the most common causes of hair loss, we can list: i) Androgenetic Alopecia (AGA), an inherited condition which is likely to appear in males [1], characterized by progressive thinning of scalp hair and defined by various patterns [2-3]. ii) Female pattern hair loss (FPHL), a diffuse reduction in hair density which affects the crown and the frontal scalp, frequently observed after puberty and affecting up to 50% of women over 50 [4-6]. iii) Telogen effluvium (TE), an intense hair shedding and diffuse thinning of hair on the scalp, usually incurring after pregnancy, stressing conditions, surgery or hormonal changes [1].

The androgen dihydrotestosterone (DHT) is thought to play a large role in inducing AGA and FPHL. DHT is formed from the conversion of circulating testosterone by 5α-reductase (5αRed); once converted it binds the androgen receptor with five times the avidity of testosterone and is more potent in its ability to cause downstream activation, this results in hair thinning on androgen-sensitive hair follicles [7,8].

There are three known isoenzymes of 5αRed receptors, types II and I play an important role in the treatment of AGA [9]. Type I 5αRed is located predominantly in the skin, including sebaceous glands and hair follicles, whereas type II is the major contributor to the DHT pool and is located in the inner root sheath of hair follicles in the scalp, beard and chest as well as the genitals and prostate gland [10].

The unique current pharmacologic therapeutic options approved by Food and Drug Administration (FDA) aimed to treat AGA, FPHL and TE are finasteride and minoxidil [11].

Finasteride is a synthetic azo-steroid that is a potent and highly selective antagonist of 5αRed type II. It is not an anti-androgen but it binds irreversibly to the enzyme and inhibits the conversion of testosterone to dihydrotestosterone. Finasteride was initially FDA approved for use in benign prostate hyperplasia (BPH), but seeing the hair growth as a side effect, it was adopted to treat AGA in 1997. The underlying principle for its use in AGA is the reduction of DHT production in order to limit its action on scalp hair follicles [12-14].

Minoxidil is a chemical compound (C9H15N5O) that has been used to treat hypertension since the 1960s [15]. Hypertrichosis as a consequence of minoxidil treatment was observed shortly thereafter and has been said to occur in 100% of the users [15,16]. These observations led to the development of topical minoxidil as a treatment for hair loss [17] and it was approved by the FDA for the treatment of male androgenetic alopecia in 1984. Minoxidil is a vasodilator that increases the cutaneous blood flow to the scalp [18] and also a potassium channel opener, which cause hyperpolarization of cell membranes, allowing more oxygen, blood and nutrients to reach the follicle [19]. Minoxidil contains an N-oxide group able to release NO, and besides being a vasodilator [20-23], it acts as a nitric oxide agonist. However, it has no therapeutic action on the hormonal and genetic causes of hair loss.

Although finasteride and minoxidil are excellent treatments, they may have side effects. Finasteride can cause fertility and libido reduction in men while hirsutism in women, furthermore, the females of childbearing age are forbidden to use finasteride due to its potential negative effects on fetus [24]. Minoxidil can cause skin redness and tachycardia [20]. Besides, these pharmacological products work only on one cause of hair loss, DHT reduction finasteride and microcirculation at follicle level minoxidil, without giving an exhaustive and complete result.

In the last ten years, it has been discovered that hair loss is not only due to hereditary factors, but also to inflammation, oxidation, hormones and vascular factors, which are involved and play a major role in the etiology of hair loss pathologies [21-24].

There are no doubts that nutrition influences hair loss and hair conditions [25,26]. Nowadays, the approach is developing natural/herbal formulation, in order to take care of these conditions by avoiding harmful side effect.

The aim of this open labels non-comparative study was to evaluate the efficacy of the nutritional complex, combining omega 3-6-9, antioxidant, natural inhibitors of 5αRed and anti-inflammatory molecules, in improving hair loss and hair health parameters such as volume, strength and reduction of greasiness.

Material and Methods

Dosage of enzyme 5αRed activity in culture of human keratinocytes (ATCC-PCS-200-010)

The experimental protocol has provided the dosage of enzyme activity marker, the dihydrotestosterone (DHT) in:

Untreated cell culture (negative control, CTR-);

Cell cultures treated with finasteride (Finasteride ≥ 98% powder from Sigma Aldrich (F12939)) 1 µg/ml, corresponding to 5 mg/day human which is the highest dose used in AGA and FPHL pharmacological treatment [27].

Cell cultures treated with *Serenoa repens* (Saw Palmetto, *Serenoa repens*, fruit fat-soluble extract (oil), ≥ 85.0% total fatty acids from NvH, Italy) 40 µg/ml, corresponding to 200 mg/day human dose, which is the most common dosage, used for hair reinforce food supplements [28].

Serenoa repens is a plant of the Arecaceae's family, also known as Saw palmetto, used in therapy for AGA. It acts as a competitive, non-selective inhibitor of 5αRed types I and II [28].

Cell cultures treated with nutritional complex (Table 1) 30 µg/ml, 60 µg/ml and 100 µg/ml corresponding to 150 mg/day, 300 mg/day and 500 mg/day human dose. This dose was established considering a medium human blood volume of 5L and assuming a total absorption of the product.

Components	Botanical name	Plant Part	Composition %
Borage OIL	*Borago officinalis*	Seed	>25<50
Linseed OIL	*Linum usitatissimum*	Seed	>25<50
Wheat GERM OIL	*Triticum vulgare*	Germ	>25<50
Saw palmetto OIL	*Serenoa repens*	Fruit	>10<25
Phytosterols from Pine EXTRACT	*Pinus sylvestris*	Bark	>0.5<5
Rye EXTRACT	*Secale cereale*	Flower	>0.5<5

Table 1: Nutritional complex components (NaturSYN Beaulixir™ kindly provided by Amitalia S.r.l, Solaro, MI, Italy).

The cells were seeded in 96-well plates at 1×10^4 cells/well and maintained at standard culture condition (37 °C in 5% CO_2).

At the end of the treatment periods respectively of 24 and 48 h, culture media were collected and stored at -80 °C until ELISA determinations were performed.

Culture media of controls and cells treated with tested product were used for the dosage of dihydrotestosterone according to ELISA method.

Commercial kits were used for the determination. ELISA uses the competitive bound between an antigen (in this case the DHT) and its primary antibody. The immune complex (antigen-antibody) was bond by a secondary antibody conjugated to a peroxidase. The addition of the enzyme substrate gives a colorimetric reaction with intensity proportional to the immune complex, providing the DHT quantity.

The quantitative determination uses a calibration curve made-up of standard known and growing concentrations of standard DHT.

Statistical analysis

An intention to treat statistical analysis was performed using NCSS 8 (version 8.0.4 for Windows; NCCS, LLC., Kaysville, UT, USA). Data were checked for normality using either the Shapiro-Wilk W, Kolmogorov-Smirnov, and D'Agostino omnibus normality tests. If the

data were normal, the repeated measure analysis of variance (RM-ANOVA) followed by Tukey-Kramer multiple comparison test was performed both intra- and inter- group comparisons. If data were not normal, the Wilcoxon signed-rank test was performed for intra-group comparisons, whereas the Mann-Whitney U test was performed for inter-group comparisons. Values are expressed as arithmetic mean ± standard deviation (SD). P value 0.05 was considered significant.

Trial design and participants

All the study procedures were carried out according to World Medical Association's (WMA) Helsinki Declaration and its amendments (Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amendments).

In order to take part to the study each participant was fully informed on study risks and benefits, aims and procedures both. Informed consent form and consent release form for the publication of photographs were signed by the subjects prior the attendance to the study.

This 6-months non-comparative, open label pilot study was conducted from January 2016 to October 2016 in Italy. The aim was to evaluate the efficacy of a nutritional supplement on hair loss and hair conditions.

Thirty patients composed of 15 males and 15 females, fulfilling the inclusion and exclusion criteria and showing at least one of the hair loss leading conditions laid down in (Table 2), were enrolled in the study. Each patient's medical history and treatment details were recorded; moreover, the clinical examination of both hair and scalp was carried out to evaluate pattern and grade of hair loss.

Inclusion and exclusion criteria
Inclusion Criteria
Healthy male and female
Age between 18 and 65 years old
Type: Caucasian race
Promise not to use any topical or systemic products designed for hair loss treatment and hair quality improvement during the study period
Promise not change the daily routine and hairstyling habits for the entire duration of the study
Exclusion Criteria
Subjects who do not fit the inclusion criteria
Subjects suffering of Alopecia Areata
Pregnant or breastfeeding women Menopausal women under hormonal therapy; Men and women with liver and / or kidney dysfunction Men who intended to have children during the six months of treatment
Hair loss leading conditions
Subjects with androgenetic alopecia grade I to IV of Norwood Hamilton scale and female pattern hair loss grade I to III of Ludwig Scale
Subjects with telogen effluvium
Subject with unbalanced diet*
Subjects with frizzy, brittle and dull hair

Table 2: Description of the inclusion and exclusion criteria for the volunteers' recruitment. Description of hair loss leading conditions ((*The daily diet was evaluated by the analysis of a "Daily diet agenda" in which the volunteer had to indicate all the meals and drinks they had during one week before the first visit. The agenda was analysed by a nutritionist. Unbalance diet: proteins<0.7 g/kg; carbohydrates>65% En; PUFA<5-10% En, PUFA n-6<4-8% En, PUFA n-3<0.5-2.0%; less than 3 portions of 50g each of vegetables a day [29]) En %=percentage of energy of the daily diet; PUFA=Polyunsaturated fatty acids; PUFA n-6=Polyunsaturated fatty acids omega-6; PUFA n-3=Polyunsaturated fatty acids omega-3).

Treatment

The enrolled patients were allocated to the treatment with an active nutritional ingredient standardized in fatty acid (≥ 90%) and phytosterols (≥ 5%) from *Serenoa repens*, *Borrago officinalis, Linum usitatissimum, Tritticum vulagare, Pynus sylvestris* and *Secale cereale* (NaturSYN BeaulixirTM kindly provided by Amitalia S.r.l, Solaro, MI, Italy) (Table 1).

This product was formulated in gelatin soft-gels containing 300 mg each.

All patients were requested to take two soft-gels of nutritional supplement every early morning for 6 months. The daily intake was monitored by a six-month calendar that was given to the volunteers at T_0 and collected at the end of six months.

Assessments

Standardized global photographs of the front/temporal and vertex region were taken, by a digital camera, at the beginning of the study (T_0), three months later (T_3) and at the end of the study (T_6). The pictures of each subject were evaluated by an expert, who assessed the

hair density through a 7-point scale following a confirmed procedure [30]:

+3 → greatly increased

+2 → moderately increased

+1 → slightly increased

→ no change

-1 → slightly decreased

-2 → moderately decreased

-3 → greatly decreased

Trichoscopic images were also obtained by Dino-Lite digital microscope and four pictures at 50x magnification were reviewed for each case.

A self-assessment questionnaire focusing on hair loss, hair density, greasiness and hair shaft conditions (strength, softness, brightness and volume) was given to all subjects at T_1, T_3 and T_6.

Further questions on the overall satisfaction of the treatment and skin and nails health were asked to all patients.

Results

In vitro

Dosage of enzyme 5-alpha-reductase activity in culture of human keratinocytes (ATCC-PCS-200-010): The results are expressed as DHT released in the media during experimental period (mean value ± dev.st.) and as mean percentage variation compared to the CTR (Figure 1).

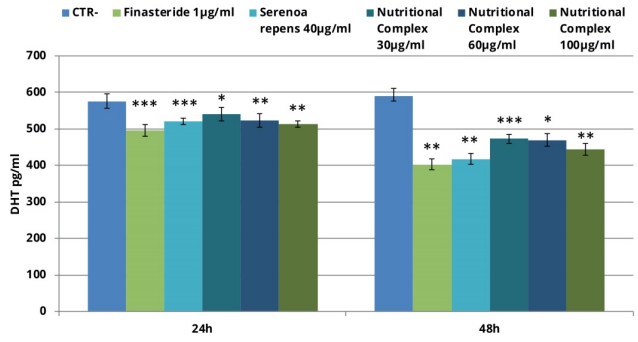

Figure 1: Dosage of DHT in cell culture at different experimental times (The results are expressed as mean value ± dev. st. (expressed in pg/ml). * Indicates a statistically significant change compared to CTR-, P<0.05; ** Indicates a statistically significant change compared to CTR-, P<0.01; *** Indicates a statistically significant change compared to CTR-, P<0.001).

After 24 h treatment, dosage of DHT in cell culture is reduced 13.9% by finasteride, 10.9% by nutritional complex at 100 µg/ml, 9.3% by the nutritional complex at 60 µg/ml, 6.1% by the nutritional complex at 30 µg/ml and 9.6% by *Serenoa repens* comparing to negative control.

Moreover, after 48 h treatment DHT is reduced 31.7% by finasteride, 24.7% by the nutritional complex at 100 µg/ml, 20.4% by the nutritional complex at 60 µg/ml, 11.3% by the nutritional complex at 30 µg/ml and 29.2% by the *Serenoa repens*, compared again with negative control.

The inhibitory activity of the nutritional complex towards the synthesis of dihydrotestosterone is time dependent, as longer is the incubation higher is the 5αRed inhibition. Moreover, the results obtained with the three different dosages of the nutritional supplement suggest that higher is the dosage stronger is the 5αRed inhibition, but further analysis needs to be done to confirm the data and to evaluate if a plateau level is going to be reached.

The product shows an inhibition of the total 5αRed comparable to both finasteride and *Serenoa repens*, especially at 24 h.

Human trial

Demography: A total of 30 patients were enrolled in the study. At baseline were defined age, hair condition, hair loss type, hairstyle, daily diet and potentials allergies for every patients, (Table 3).

Subjects, N=30	Age (years, mean ± SD)	Androgenetic alopecia/female pattern hair loss (N)	Severe telogen effluvium (N)	Stress and food deficiency hair loss (N)
Male, N=15	35.9 ± 10.8	9	3	3
Female, N=15	36.9 ± 10.9	3	10	2

Table 3: Demography of volunteers.

The female group was composed of: 2 post-breastfeeding women, 4 ladies in post-menopause and 9 girls of child breading age; 3 of them suffers of FPHL, 10 of telogen effluvium and 2 of stress or nutritional deficiencies hair loss. The male group was made up of: 6 men aged in between 20 and 30 years old, 5 in between 30 and 40 years old and 4 over 40; 9 of them suffers of AGA, 3 of severe telogen effluvium and 3 of stress or nutritional deficiencies hair loss.

All the 30 patients finished the study. The compliance was calculated form the daily calendar collected that the end of the study: 85% took all the requested capsules, 8% forgot the capsules for 1 to 2 days, 5% forgot them for 2 to 5 and 2% forgot to take the nutritional supplement for more than 5 days in the whole six months.

Trichoscopy: The analysis conducted through digital microscope show an improvement of hair density and new hair growth after 6 months treatment (Figure 2 above and below). Furthermore, an improvement of vascularization and reduction of greasiness at the follicle level have been evaluated (Figure 2 below and middle). These partial and macroscopic results need to be reconfirmed in a future study by software measurements of hair density and shaft.

In addiction has been noted that, women who experienced the reduction of greasiness, 93% of the volunteers, went through a reduced hair-washing tendency per week passing form four to three times a week, 56%, and from three to two times a week, 44%. This condition was not evaluated by the men as all the enrolled wash their hair daily.

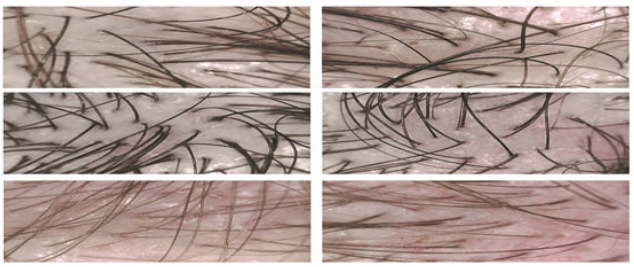

Figure 2: Trichoscopy of subjects 25 (above), 20 (middle) and 14 (below) at Time zero (left) and after 6 month of treatment (right).

Global photograph review: Photographs review and analysis show an interesting improvement of hair density already at T_3; however, the major variances can be appreciated at T_6. After 6 month treatment 83.3% of subjects experience an increased hair density (Table 4). Reference photographs are shown in Figure 3.

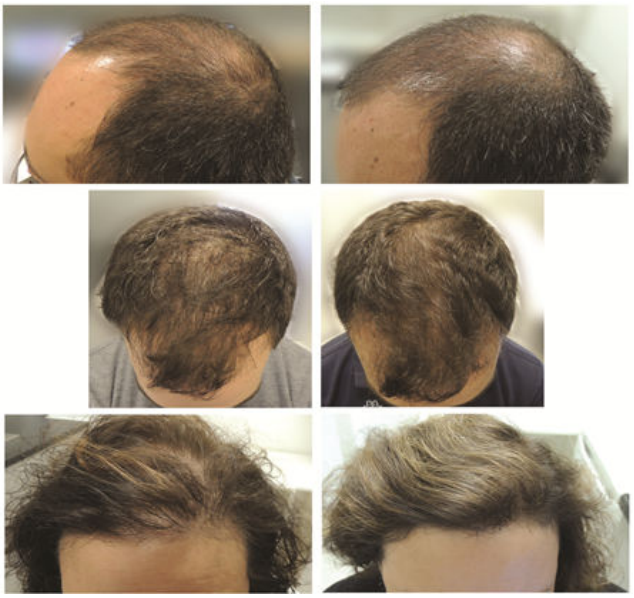

Figure 3: Global photographs of subjects 26 (above), 11(middle), 29 (below) at Time zero (left) and after 6 month of treatment (right).

Hair Density	Male N=15 (%)	Female N=15 (%)	Tot N=30 (%)
-3: greatly decreased	0	0	
-2 moderately decreased	0	0	
-1 slightly decreased	6.7	6.7	6.7
0 no change	13.3	6.7	10.0
1 slightly increased	20.0	26.7	23.3
2 moderately increased	33.3	26.7	30.0
3 greatly increased	26.7	33.3	30.0

Table 4: Change in hair density T6/T0 evaluated by global photography, expressed in % respect to the total component of the group.

Subject's assessment: Hair quality and hair loss reduction valued by the subjects show positive results confirming the photographic outcomes.

Some positive effects are already felt after one and three months of supplementation, but is at T_6 that the volunteers experienced the best results.

After 6 month treatment 93.3% of the subjects see a general reduction in hair loss and 79.0% of them define it as significantly high; 83.3% notice a thicker and bulky hair; 90.0% feel the hair stronger with a better combing effect; finally, 88.5% experience a reduction of greasiness. Only few of them see an improvement in hair softness and brightness (Table 5).

	T_1	T_3	T_6
Overall hair loss is decreased	80	83.3	93.3
Hair volume is improved	76.7	73.3	83.3
Hair density is improved	73.2	77.0	84.1
Hair softness is improved	15.3	18.2	17.8
Hair strength is improved	73.3	70.0	90.0
Hair brightness is improved	10.1	10.5	11.6
Hair greasiness is reduced	78.6	83.3	88.5

Table 5: Self-assessment questionnaire (% of subject in agreement (totally agree, agree and slightly agree) with the statement).

As secondary outcomes, 89.3% of subjects highlight an improvement of nails strength and 72.4% notice a reduction of skin greasiness and redness (data not shown).

At the end of the study, 93.0% of subjects are satisfied with the results. The product is well tolerated, with a good mouth feel and without any adverse event reported.

Discussion

As demonstrated in the last decade of studies and by the hospital practices, hair loss/ hair disorders have multifactorial etiology. It is commonly accepted that 5αRed activity is not the only pivotal point in hair pathology; indeed, follicular micro inflammation, oxidation and microcirculation at the hair bulb are the leading causes of these conditions [31-33]. Furthermore, the lack of immunity defense or nutritional deficiencies can increase the seriousness or enhance the disorders [34].

For these reasons, a nutritional supplement working on just one aspect of this complex pathology is not enough. A formulation carrying omega 3-6, antioxidant, phytosterols and vitamins can approach the multifactorial nature of this problem, instead.

Phytosterols, in particular ß-sitosterol, have demonstrated their capacity to inhibit 5αRed type I and II, which is responsible of

the conversion of testosterone into dihydrotestosterone, worldwide recognized as one of the major players in hair miniaturization, leading to AGA or FPHL [35-37]. In this formulation, the phytosterols are mutually provided by saw palmetto, pine bark and rye grass extracts.

Not only phytosterols can inhibit the 5αRed activity, but also omega-3 polyunsaturated fatty acid (PUFAs) and omega-6 (linolenic acid (LA) and γ-linolenic acid (GLA)), which can be found in very high concentration in linen seeds, borage oil, *Serenoa repens* and wheat germ oil [38].

Omega-3 and omega-6 have been studying for their potential activity on hair loss and hair condition for more than 20 years [39]. They are reported to exert an anti-oxidant activity and to reduce inflammation by directly influencing the arachidonic cascade. Furthermore, through the incorporation into the cell membrane they give a big help to the cell growth, regeneration and tissue fluidity [40].

Give that oxidation is now seen as one of the most important players in hair ageing process [41] and consequent discomfort, a big effort has been done to select ingredients highly standardized in phytosterols such as specifics pine bark and rye extract. Moreover, rye extract was demonstrated to stimulate the immune system by inducing the anti-inflammatory reactions and treating another cause of hair disorders.

The preliminary part of the study, conducted *in vitro*, demonstrate that this formulation can exert an inhibition of the total 5αRed comparable to finasteride and *Serenoa repens*, especially at 48 h. The inhibitory activity of the nutritional complex towards the synthesis of dihydrotestosterone is time dependent, as longer is the incubation higher is the 5αRed inhibition. These results prove the inhibitory activity of a natural combination of phytosterols and omega 3-6 from *Serenoa repens*, linseed, borage, wheat oils, pine bark and rye grass on 5αRed.

The nutritional complex, where *Serenoa repens* is present in less than 100 mg/daily dose, eliminates regulatory issues in that countries where *Serenoa repens* is allowed only within 140 mg/day, in the meanwhile provides an active complex composed of anti-inflammatory, anti-oxidant and immunomodulator molecules at once.

The human study shows the positive effects of this natural complex supplementation on overall scalp coverage by an improvement of vascularization, hair diameter, strength and volume and a reduction of hair loss perception. These outcomes are clearly visible from the trichoscopy and global photographs review comparing T_0 and T_6.

Both the reduction of hair greasiness (revealed by the trichoscopy and self-assessment) and the improvement of hair quality (visible in the pictures and confirmed by the subject's assessment) demonstrate that this formulation is not only effective against 5αRed but it also exerts its properties in a complete manner by restoring the physiologic condition of the healthy scalp. Significant there is also the improvement of nails strength and the reduction of skin redness and greasiness. These results confirm how the systemic activity specifically targets hair, skin and cutaneous annexes.

This is only a preliminary study, which provides interesting inputs on the effectiveness of the formulation complex standardized in fatty acids and phytosterols against hair loss and hair disorders: the positive response encourages to deepen the studies and to carry on a further randomized and placebo controlled study.

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