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A Randomized, Double-Blind, Placebo-Controlled Study of a Nutraceutical Supplement for Promoting Hair Growth in Perimenopausal, Menopausal, and Postmenopausal Women With Thinning Hair

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ABSTRACT

Hair loss is a complex and multi-factorial problem that is associated with significant psychological morbidity in women. Menopausal women represent a significant percentage of those affected, since the menopausal hormonal transition can be a contributing factor. A novel nutraceutical supplement has been specifically formulated with phytoactives to improve hair growth and quality in menopausal women (Nutrafol® Women's Balance Capsules).

The objective of this 6-month, randomized, double-blind, placebo-controlled study was to assess the safety and efficacy of this oral supplement to promote hair growth in perimenopausal, menopausal, and postmenopausal women with self-perceived thinning. Subjects were randomized to the study supplement (n=40) or placebo (n=30). The primary endpoint was a statistically significant increase in the number of terminal and vellus hairs based on phototrichogram analysis. Daily intake of the nutraceutical supplement resulted in progressive and significant increase in terminal and total hair counts on days 90 (P<0.01) and 180 (P<0.01) compared to placebo. The vellus hair counts significantly increased for the active treatment group (P<0.05) by day 180 while significantly decreasing for the placebo group subjects. Hair shedding progressively and significantly decreased for the active group compared to placebo, culminating in a reduction of 32.41% by day 180 (P<0.01). The study supplement was well-tolerated.

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INTRODUCTION

Hair loss occurs in women almost as frequently as men, affecting at least 50% of women by age 50.[1-5] A recent review on psychological and aesthetic impact of age-related hair changes in women showed hair loss to demonstrably affect a woman's perceived age and psychosocial wellbeing.[6] Increasing with age and menopause,[7] the most commonly diagnosed alopecia is female pattern hair loss (FPHL), also known as androgenetic alopecia (AGA), which affects an estimated 40% of women over 60.[8] The complex pathophysiology of FPHL is not yet fully elucidated, but is now considered to be only partly related to androgens, with growing evidence suggesting it's multifactorial.[9] Some attribute the increase in FPHL and generalized diffuse hair loss in postmenopausal women to normal physiological changes of menopause and aging.[7,10] Hormonal changes in menopause include a rapid decline of ovarian estrogens and a relative increase in androgens.[7,11]

Consequently, hormonal changes of menopause are associated with decreased growth rate, percentage of hairs and time spent in anagen, a decrease in hair diameter and change in diameter distribution,[11] as well as increased miniaturization.[7,10] There are likewise age-related changes in hair diameter and density that are independent of menopause, but occur at approximately the same time, compounding the perception of hair loss for middle-aged women.[6,11] Hair loss and thinning in women is polygenic and multi-factorial, with contribution from environmental factors such as aging, stress, and inflammation.[4,6,9] Nevertheless, there is a paucity of controlled studies assessing interventions for hair thinning in menopausal women. Options are limited and have been developed to address singular targets, as exemplified by androgen-inhibiting therapies (eg, finasteride, spironolactone, etc), which are often used off-label for women after childbearing years.[6,9] So far, results from studies on finasteride and spironolactone have been inconsistent, showing varied efficacy in post-menopausal women.[6,9] Currently, the only FDA-approved drug for treatment of hair loss in women is topical minoxidil, which has potential side effects and many women find difficult to incorporate into daily haircare routines.[5,12]

A novel nutraceutical supplement has been specifically formulated to provide a multi-targeted approach to thinning hair in women going through the menopause transition (NUTRAFOL® Women's Balance, Nutraceutical Wellness Inc., New York, NY). The formulation features the patented Synergen Complex Plus®, a combination of standardized botanicals with clinically tested stress-adaptogenic, antioxidant, anti-inflammatory, dihydrotestosterone (DHT)-inhibiting, and hormone-balancing properties. These featured phytoactives include extracts of saw palmetto, maca, astaxanthin, curcumin, tocotrienols, and ashwagandha – all bio-optimized for enhanced bioavailability.[12]

Here, we present the 6-month interim results of a 12-month, randomized, double-blind, placebo-controlled study assessing the safety and efficacy of this novel nutraceutical supplement in improving growth of hairs (terminal and vellus) in perimenopausal, menopausal, and postmenopausal women with self-perceived thinning hair. To our knowledge, this is a first published study on the use of supplements for hair thinning in women going through the menopausal transition.

METHODS

Study Subjects

Study participants were healthy female subjects, 40 to 65 years old, with self-perceived thinning hair, as confirmed by a board-certified dermatologist investigator. Subjects were perimenopausal, menopausal or postmenopausal with Fitzpatrick I–IV photo skin types. Perimenopausal was defined as increased variability in menstrual cycle length and characterized by a persistent difference of ≥7 days for consecutive cycles. Later stages included amenorrhea for ≥60 days and/or vasomotor symptoms present for >6 months prior to the study. Menopause was defined as absence of menstrual bleeding for ≥12 months or 12 months status post-hysterectomy with oophorectomy. Enrolled subjects agreed not to substantially change their diet, medications, exercise, hair shampooing routines, and maintain a consistent frequency of haircut and color treatments for the duration of the study. The study was approved by an institutional review board and conducted in accordance with the accepted standards for Good Clinical Practices. All participants provided written informed consent prior to participating.

Reasons for exclusion from study included: allergy or sensitivity to any shampoo or conditioner; a stressful incident within the last 6 months (eg, death in family); recent (<6 months) initiation of hormone replacement therapy (HRT); current use of treatments for thinning hair such as low level laser therapy (LLLT) or minoxidil within the last 3 months; use of other medications that are known to cause hair loss or affect hair growth within the last 6 months (eg, spironolactone, cyproterone acetate, finasteride, or any 5-alpha-reductase inhibitors). Subjects with a known or self-reported history of uncontrolled disease in the opinion of the investigator (eg, autoimmune disorders, thyroid disease, diabetes); documented iron deficiency, bleeding/platelet disorders, on anticoagulant/antiplatelet therapy or >325mg aspirin daily were excluded, as well as any subjects with a known history of malignancy (except squamous or basal cell carcinoma). Other reasons for exclusion were presence of other hair loss disorders as diagnosed by the investigator, as well as active dermatoses or other health conditions which, in the opinion of the investigator, might place the subject at greater risk or interfere with clinical evaluations.

Test Material

The nutraceutical supplement used in this study (NUTRAFOL® Women's Balance Capsules, Nutraceutical Wellness Inc., New York, NY) contains a patented Synergen Complex Plus®, a proprietary blend of clinically tested, standardized and bio-optimized phytoactive extracts, in addition to other botanicals, vitamins, and minerals. Some of the key ingredients include standardized extracts of curcumin, ashwagandha, saw palmetto, maca, astaxanthin, tocotrienol-rich tocotrienol/tocopherol complex, capsaicin and piperine, as well as hydrolyzed marine collagen and organic kelp. Placebo capsules consisted of inert material with same appearance. Subjects were instructed to take a dose of four capsules of their assigned therapy with or immediately following a meal, at approximately the same time daily.

Study Procedures

This was a 6-month randomized, double-blind, placebo-controlled trial with a 6-month open label extension phase. The first part of the study consisted of three clinic visits at baseline, day 90, and day 180. The investigator performed a basic physical examination at each visit, including a basic body systems overview, vital signs, and scalp assessments. At the initial visit, the scalp was examined by the investigator to rule out any confounding scalp conditions. Subjects were also queried on general lifestyle practices, including diet, stress, alcohol, smoking, and exercise. A target area was chosen along the frontalis bone, the anterior lateral triangle of the scalp where the lateral and frontal hairlines meet. The location was recorded for future assessments using triangular three-point measurements obtained from the medial canthus, lateral canthus, and preauricular skin pit to the hairline junction. Where these three points met, an approximately 1 cm^2 target area was marked and monitored.

Phototrichograms were obtained of the target area during each visit via macrophotography (Canon Power Shot G16 with 3GEN Dermlite FOTO Pro Dermoscopy DSLR lens) for hair count analysis of terminal, vellus, and total hairs. To measure hair shedding, subjects were instructed to wash their hair at home 24 hours in advance of each study visit. At the time of the visit, subjects' hair was washed with a gentle shampoo over a cheesecloth-covered sink to collect shed hairs, which were counted and recorded.

During each clinic visit, 2-dimensional standardized global photographs (7 views) were obtained of the entire head, hair and target region (IntelliStudio®, Canfield Scientific; Parsippany, NJ). Two-dimensional images were used for informational purposes and to assist in grading general hair growth and hair quality assessments. At day 90 and day 180 visits, the blinded investigator completed assessment of Global Hair Growth and Global Hair Quality Improvement (texture, shine, dryness, scalp coverage, hair brittleness, and overall appearance) from baseline. Scoring was based on a 7-point scale with a range of -3 = greatly worsened to +3 = significantly improved.

The Women's Hair Loss Quality of Life Questionnaire,[13] QOL Subject Hair Satisfaction Questionnaire, and Menopause Rating Scale Questionnaire[14] self-assessments were administered at all visits, while Self-Assessment Questionnaire, Subject Treatment Satisfaction, and Ease of Use Questionnaire at 3 and 6 months.

Study Endpoints

The primary efficacy endpoint from phototrichogram analyses was the change in the number of terminal, vellus, and total hairs at day 90 and day 180. Secondary endpoints were change in hair shedding counts, change in blinded physician global hair assessments for hair growth and quality, and responses on subject self-assessments.

Statistical Analysis

Descriptive analyses initially examined the distribution and characteristics of variables to summarize the study population. Continuous measures were evaluated across visits and comparing treatment groups using parametric Analysis of Variance (ANOVA) test. Categorical measures were evaluated descriptively and using the non-parametric Fisher's exact test.

TABLE 1.

Subject Demographics and Baseline Characteristics			
	Active (n=33)	Placebo (n=27)	All (n=60)
Mean Age (SD), years	54.6 (5.9)	55.8 (7.3)	55.2 (6.6)
Age Range, years	43 - 64	40 - 65	40 - 65
Race/Ethnicity, n (%)			
Caucasian	20 (61)	20 (74)	40 (67)
Hispanic	9 (27)	3 (11)	12 (20)
Asian	3 (9)	2 (7)	5 (8)
Pacific Islander	1 (3)	1 (4)	2 (3)
Hispanic/Armenian	--	1 (4)	1 (2)
Fitzpatrick Skin Type, n (%)			
I	3 (9)	3 (11)	6 (10)
II	13 (39)	10 (37)	23 (38)
III	12 (37)	9 (33)	21 (35)
IV	5 (15)	5 (19)	10 (17)

All analyses were two-tailed, where applicable, with P-value of <0.05. Analyses were performed using a commercial statistical package (GraphPad Prism 8.4.3. San Diego, CA. Released 2020).

RESULTS

Subject Demographics and Baseline Characteristics

Seventy female subjects were enrolled and randomized to receive active treatment (n=40) or placebo (n=30). The interim analysis is based on 60 (33 active and 27 placebo) per protocol population who completed the 6-month randomized phase of the study. Subjects had an overall mean age of 55.2 (6.6 SD) years with no significant differences between groups. Demographics and baseline characteristics are summarized in Table 1. Most subjects were post-menopausal (58%) with about one-half (47%) experiencing menopause symptoms, which was comparable between active (48%) and placebo groups (44%). The two most frequently reported menopause symptoms were hot flashes (61%) and irregular menses (43%) (Table 2). Most subjects reported symptom frequency as sporadic but a few experienced symptoms as often as 4–5 times weekly. Subjects reporting hot flashes indicated they tend to occur daily. Among subjects receiving thyroid medication (n=14), most were randomized to the active treatment group (n=12); however, a sub-analysis of covariance performed on the total hair count data determined this difference in thyroid medication had no impact on the primary endpoint.

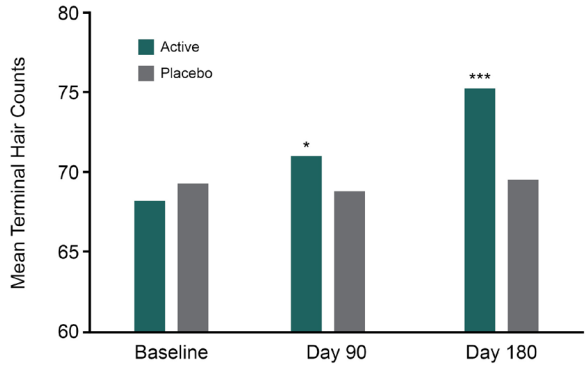
Primary Endpoints

Among subjects in the active treatment group, terminal hair counts (Figure 1) and total hair counts (Figure 2) progressively and significantly increased on days 90 (P<0.01) and 180 (P<0.01) compared to placebo. The increase in terminal hair counts translated into a significant improvement of 4.3% by day 90 and 10.2% by day 180 from baseline for the active treatment group vs a negligible change of -0.2% and 0.7%, respectively, for the placebo group. Total hair count improvements translated into

TABLE 2.

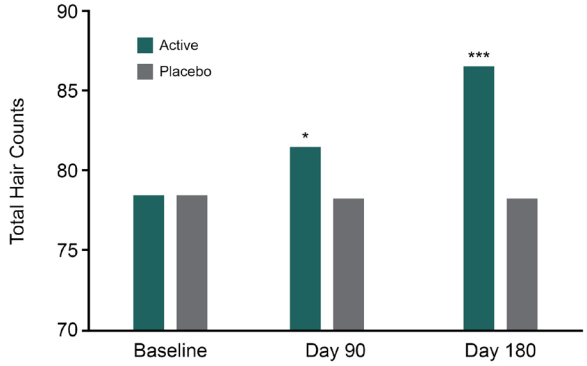
Menopausal Status and Symptoms			
Status, n (%)	Active (n=33)	Placebo (n=27)	All (n=60)
Perimenopausal	8 (24)	6 (22)	14 (24)
Menopausal	8 (24)	3 (11)	11 (18)
Postmenopausal	17 (51)	18 (67)	35 (58)
Menopause Symptoms, n (%)			
Hot flashes	9 (56)	8 (67)	17 (61)
Irregular menses	5 (31)	7 (58)	12 (43)
Night sweats	5 (31)	4 (33)	9 (32)
Mood swings	1 (6)	4 (33)	5 (18)
Absent menses	2 (13)	--	2 (7)
Insomnia	1 (6)	--	1 (4)

FIGURE 1. Among subjects in the active treatment group, terminal hair counts progressively increased on days 90 and 180.



*denotes $P<0.01$, ***denotes $P<0.01$.

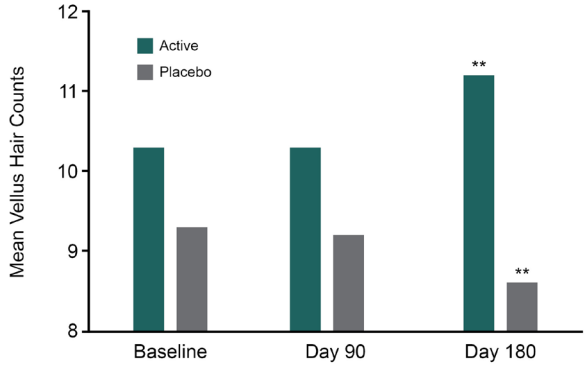
FIGURE 2. Among subjects in the active treatment group, total hair counts progressively increased on days 90 and 180.



*denotes $P<0.01$, ***denotes $P<0.01$.

3.7% by day 90 and 9.97% by day 180 for the active treatment group compared to -0.2% and -0.2%, respectively, for the placebo group. The vellus hair counts significantly increased for the active treatment group ($P<0.05$) by day 180 while significantly decreasing for the placebo group subjects (Figure 3), translating into a significant percent change of 10.78% and -3.38%, respectively. The mean target area hair counts for these endpoints are summarized in Table 3.

FIGURE 3. By day 180, the mean vellus hair counts significantly increased for the active treatment group while decreasing for the placebo group.



**denotes $P<0.05$.

Secondary Endpoints

Hair shedding count progressively and significantly decreased among active group subjects culminating in a decrease of about one-third (-32.41%) by day 180 relative to baseline ($P<0.01$). Conversely, the percentage change in shed counts initially increased for placebo group subjects and then decreased at day 180 relative to baseline by -10.08% and did not reach statistical significance (Table 4; Figure 4).

Blinded investigator global hair assessments showed a progressive and significant improvement for the active group compared with the placebo group at day 180 on both hair growth and quality scales. Global hair growth improvement ratings were recorded for 30% of active group subjects at day 90 and for 73% at day 180, while only 11% of placebo group subjects received global hair growth improvement ratings at day 90 and 22% at day 180. The difference in improvement ratings between treatment groups on day 180 was significant ($P<0.05$; Figure 5). Global hair quality improvement ratings were also significantly different between active (42%) and placebo (15%) groups at day 180 ($P<0.05$; Figure 6).

Seventy-three percent of subjects in the active group were satisfied (either slightly, moderately, extremely) with their treatment at day 180. Self-Assessment questionnaire revealed that 30% of subjects in the active group reported a 2-point

TABLE 3.

Mean Target Area Hair Counts						
Group, mean (SD)	Active, n=33			Placebo, n=27		
	Day 0	Day 90	Day 180	Day 0	Day 90	Day 180
Terminal Hairs	68.1 (6.5)	71.0 (7.5)[a]	75.1 (9.1)[a]	69.2 (6.7)	68.9 (6.7)	69.5 (9.1)
Vellus Hairs	10.3 (2.2)	10.3 (1.9)	11.2 (1.6)[b]	9.3 (9.1)	9.2 (1.5)	8.6 (1.3)[b]
Total Hair Count	78.4 (7.4)	81.3 (8.4)[a]	86.3 (10.2)[a]	78.4 (7.7)	78.2 (7.6)	78.1 (7.5)

[a]$P<0.01$; [b]$P<0.01$

FIGURE 4. Active treatment resulted in a progressive decrease in shed hair counts across visits, amounting to -21.6 hairs (-32.41%) by day 180 relative to baseline ($P<0.01$).

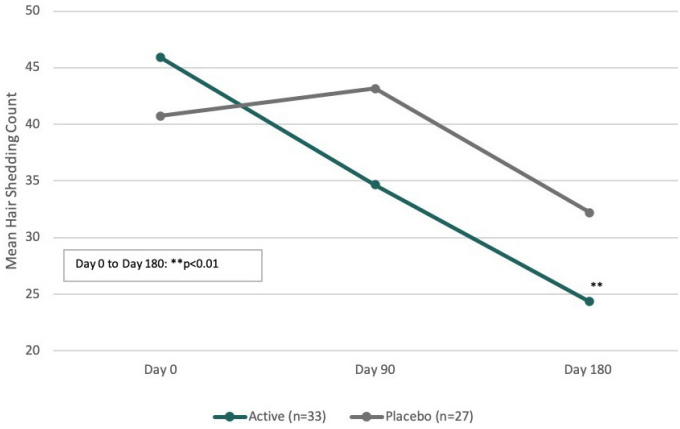


TABLE 4.

Mean Hair Shed Counts			
Group, mean (SD)	Active, n=33		
	Day 0	Day 90	Day 180
Active (n=33)	45.9 (40.9)	34.6 (36.1)	24.3 (14.1)[a]
Placebo (n=27)	40.7 (21.2)	43.2 (32.2)	32.2 (17.9)

[a]$P<0.05$

(moderate) improvement for overall hair growth, hair volume and scalp coverage at day 180 compared to none in the placebo group. Hair Loss Quality of Life Questionnaire showed that hair thinning affected the self-esteem of all menopausal subjects at baseline and that by day 180, thirty-eight percent of the subjects in the active group no longer reported this concern. The majority of subjects in the active group responded positively to questions regarding ease of use with 97% reporting ease of adding the capsules to their daily routine, 94% reporting convenience of taking the capsules once daily instead of applying a topical

FIGURE 5. Percentage of positive investigator hair growth ratings. By day 180, Investigator Global Hair Growth Assessments showed a progressive and significant improvement for the active group compared with the placebo ($P<0.005$).

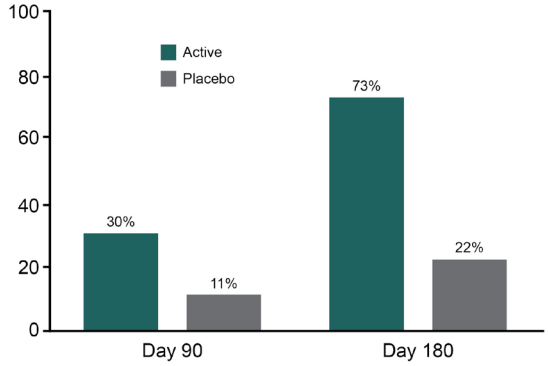


FIGURE 6. Percentage of positive investigator hair quality ratings. By day 180, Investigator Global Hair Quality Assessments showed a progressive and significant improvement for the active group compared with the placebo ($P<0.05$).

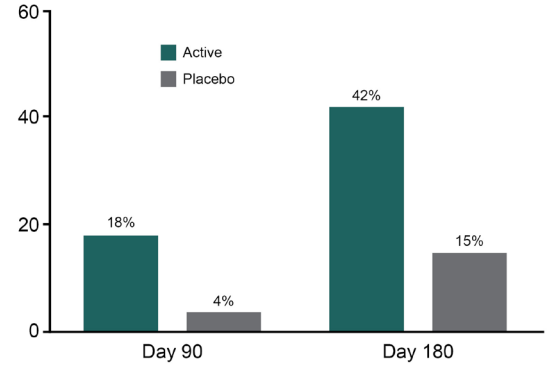
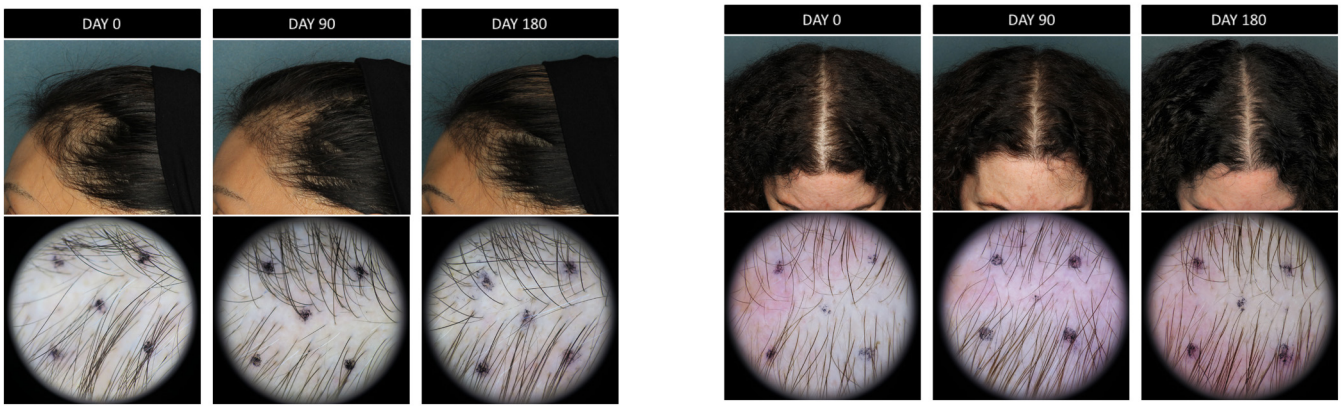


FIGURE 7. Improvement in hair growth for 2 representative subjects treated with the active product. **Top Row:** Global photographs showing visible clinical improvement. **Bottom Row:** Macrophotographs of selected target areas.



product to the scalp once or twice daily, and 91% feeling more comfortable taking a natural supplement. Seventy-six percent of active-treated subjects would recommend the product.

Safety

No unanticipated adverse events were reported. Adverse events occurred in three subjects, two in the active group (nausea, bloating, diarrhea) and one in the placebo group (nausea, headache).

DISCUSSION

The results of this six-month interim analyses showed that the administration of a novel oral supplement with patented Synergen Complex Plus® in perimenopausal, menopausal, and postmenopausal women with thinning hair was effective compared to placebo. Total hair counts, terminal hair counts, vellus hair counts, and shedding all significantly improved compared to placebo. These parameters were supported by significant and progressive visible clinical improvement in both hair growth and hair quality for the treatment group, as determined by a blinded investigator.

Subjects in the placebo group showed no significant improvements for the same hair parameters. In fact, vellus hairs were significantly decreased among subjects in the placebo group, which could indicate progressive change in hair during menopausal transition, normally marked by relative androgen dominance.[7,11] It is known that androgens are converted to DHT via 5α-reductase at the follicle, where it shortens the anagen phase and causes miniaturization from terminal to vellus-like hairs in genetically predisposed follicles.[6,7] Although a decrease in vellus hairs could also indicate the transition of those hairs to terminal ones, the concomitant lack of increase in terminal hairs for placebo subjects suggests otherwise. Miniaturization of follicles and hair loss tend to be progressive without intervention.[2] These results suggest that progressive menopausal changes in hair may be reduced or at least delayed with intervention that specifically addresses hormonal changes in menopause.

While the full etiology of many types of hair loss remains elusive, research has shown that especially in women it is multi-factorial.[4] Various molecular pathways and factors including DHT, aging, oxidative damage, inflammation, hormonal fluctuation, as well as stress mediators, play a significant role in compromising the hair follicle.[4,9] Nutraceuticals providing multi-modal biological activity against these molecular and environmental factors therefore offer a unique therapeutic value. For example, standardized ashwagandha has anti-inflammatory, antitumor, stress-adaptogenic, antioxidant, and immunomodulatory activity[15] and has demonstrated benefits in women with mild to moderate symptoms of menopausal syndrome.[16] It was likewise shown to lower elevated cortisol levels in stressed adults.[17] Standardized curcumin is a major component of turmeric with known anti-inflammatory and anti-oxidative effects, and was demonstrated to improve endothelial function in postmenopausal women.[18] The biological and clinical activity of these ingredients has been previously detailed in a recent review by Farris et al.[12] Moreover, these nutraceutical grade extracts along with other ingredients make up a similar formulation that was shown to significantly improve hair growth and quality compared to placebo in women with thinning hair.[5]

The currently studied formulation contains optimized dosages and added botanical ingredients, selected to address specific additional targets of hair thinning in women going through and beyond the menopausal transition. These targets include the relative hormonal shifts that occur in menopause. Paradoxically, most women that experience hair thinning in menopausal years have normal levels of androgens, but experience a decline in ovarian estrogens.[11] Ultimately, the local balance of these hormones metabolized at the follicle influences hair growth by signaling a number of other hormones, transcription factors, growth factors, and cytokines.[11] In addition to declining estrogen levels in relationship to androgens,[11] other significant changes which affect the hair follicle specifically through and after menopause include: increased oxidative stress and inflammation,[19] stress-related increases in cortisol,[20,21] metabolic changes,[22] and changes in nutritional status.[23]

One key ingredient is saw palmetto, which has shown efficacy in hair loss,[24,25] and is known for its well-documented anti-androgenic and DHT-inhibiting[26] properties. The dosage was optimized and increased in this formula. Maca root contains numerous constituents, including an alkaloid lipidiline, which exerts a positive effect on balance of endogenous sex hormones through its activity on 17β-hydroxysteroid dehydrogenase.[27] Administration of maca has been shown to significantly improve menopausal symptoms.[28] It also has adaptogenic effects, reducing stress-induced corticosterone levels,[29] and targets DHT.[30] Astaxanthin is an antioxidant 600-times more potent than vitamin C. It possesses anti-inflammatory and antioxidant properties, improving oxidative status overall and in aging skin.[31,32] In the current study, the daily use of this blend of nutraceutical-grade extracts significantly increased the number of terminal and vellus hairs in perimenopausal, menopausal, and post-menopausal women. To our knowledge, this is the first prospective study showing clinical efficacy of a nutraceutical supplement in improving hair growth in women with thinning hair in menopausal transition.

A previous study evaluating an earlier formulation for women showed similar objective progressive improvements in hair growth and hair quality at 3 and 6-months.[5] A significant percentage of subjects taking the supplement reported improvements in hair parameters, such as hair growth, thickness, and overall hair volume.[5] The subjects in the current study also reported progressive improvements based on self-

assessment questionnaires, suggesting sustained and perhaps even enhanced improvement may occur with continued use. This hypothesis, along with other potential long-term benefits of the nutraceutical, will be evaluated in the six-month open-label extension phase of the current study scheduled to be completed by 2020.

The supplement was well-tolerated. An overwhelming majority of subjects taking the active product not only found it to be more convenient to incorporate into their daily routine over using a topical application, but also preferred taking a natural alternative – underscoring the need for efficacious nutraceutical formulations. Furthermore, this emphasizes the importance of selecting tailored supplements that have clinical data on phytoactivity, bioavailability, standardized dosing, bio-optimization, and potency.[12]

CONCLUSION

The results of this study demonstrate the ability of a novel nutraceutical supplement with bio-optimized phytoactive ingredients to safely and effectively improve hair growth and quality in perimenopausal, menopausal, and postmenopausal women with thinning hair. The number of total, terminal, and vellus hair counts, and hair shedding all significantly improved compared to placebo. Investigator global ratings for hair growth and quality were significantly higher for subjects in the active treatment group compared to placebo. The supplement was found to be well-tolerated, safe, and easily incorporated into daily routines.

DISCLOSURES

Dr. Glynis Ablon received a research grant for the study. Dr. Sophia Kogan is a researcher at Nutraceutical Wellness, Inc.

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