A Novel Multi-Targeting Approach to Treating Hair Loss, Using Standardized Nutraceuticals

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ABSTRACT

Hair loss is a complicated problem that causes significant concern for those who are affected. Patients seeking medical treatment have limited options that include topical minoxidil and oral finasteride. While these treatments are backed by long term clinical use and research outcomes, many patients find topical minoxidil difficult to incorporate into their daily routine and some are concerned with the side effects associated with finasteride. In the office setting, patients may be treated with more invasive procedures such as platelet-rich plasma injections (PRP) and hair transplantation, treatments that often must be repeated and can lead to a costly investment.

Consumers are increasingly interested in natural treatments for hair loss. Many turn to basic supplements only to be disappointed when they fail to deliver due to lack of standardization and efficacy. In this paper we review the benefits of a nutraceutical containing a specific blend of highly purified, standardized, bio-optimized, and bioavailable botanical extracts to treat hair loss. These phytoactives were selected because of their diverse multi-modal biologic activity against inflammation, DHT, stress mediators, oxidative damage, and intermediary signaling cascades. This supplement represents a paradigm shift as it addresses not only the factors that trigger hair loss but the downstream mediators of inflammation as well. Multi-center clinical studies are currently underway to confirm the efficacy and benefits of this unique nutraceutical.

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INTRODUCTION

Nutraceuticals are an emerging category of beauty products and one of the fastest growing segments in the nutricosmetic market.[1] This class of naturally derived therapeutics from food and botanicals contain *phytochemicals - biologically active compounds* that protect or promote health and occur at the intersection of food and medicine. Driving nutricosmetic sales is the growing acceptance of an inside-out-approach to health and beauty and the fact that these nutraceuticals are viewed as safe and natural. Nutritional alternatives and supplements to treat hair loss are among the most sought after nutricosmetics. Healthy hair requires more than just balanced nutrition so it follows that many patients who experience hair loss turn to nutraceuticals.[2]This emerging category distinguishes itself by attributing efficacy to the isolation and standardization of specific phytochemicals that have clinically studied therapeutic effects. It is important to note that while nutritional supplements are regulated by the FDA and FTC, they are not subjected to the same rigorous standards as drugs.[3] Nutraceuticals that lack standardized dosing, potent and pure ingredients, or contain phytoactives that are not bioavailable may be ineffective. For this reason, it is imperative that dermatologists are knowledgeable and able to guide their patients on nutraceutical selection.

The most common form of hair loss, androgenetic alopecia (also termed female and male pattern hair loss), affects at least 40% of women and 50% of men and will progress without treatment.[4] Patients who suffer with hair loss often develop depression and anxiety that is precipitated by the fact that there is no cure for hair loss and available medical treatments take months to produce variable results.[5,6,7] Currently, there are only two drugs that have been FDA approved for treating hair loss.[8] Topical minoxidil, now available over the counter in 2% and 5% solutions and 5% foam, is approved for use in both men and women.[9] The exact mechanism of action of minoxidil is uncertain but it is known to prolong the anagen phase of hair growth and increase blood supply to the follicle.[10] Finasteride is a type II 5-alpha reductase inhibitor that prevents conversion of testosterone to its active form 5-dihydrotestosterone (DHT).[11] Finasteride slows the progress of hair loss and stimulates regrowth in patients with androgenetic alopecia. While both medications are supported by clinical studies and long-term clinical use, they are not without limitations. Topical minoxidil is objectionable to many who find the application process difficult to incorporate into a daily hair-care routine. Women may suffer side effects particularly with higher dose minoxidil including the growth of facial hair.[12] Irritant or allergic contact dermatitis can occur with minoxidil solution and is attributed to the propylene glycol used to solubilize minoxidil.[13] The use of finasteride is limited to men and, off-label, post-menopausal women as ingestion of finasteride

during pregnancy can result in deleterious effects on a male fetus including ambiguous genitalia.[14] While generally well-tolerated, finasteride may also have side effects concerning for male patients, most notably sexual dysfunction. In limited cases, sexual dysfunction may persist in association with depression, melancholy, and general loss of general well-being.[15,16,17] This well-publicized disorder, which has been termed post-finasteride syndrome (PFS) has resulted in some male patients refusing finasteride therapy. Finally, both minoxidil and finasteride must be used indefinitely because discontinuation results in regression and progression of alopecia.[8] Accordingly, it is not surprising that many who suffer with hair loss seek alternatives to these medications.

The pathogenesis of all forms of hair loss is multifactorial and requires a multi-modal solution. Treatments targeting only one mechanism may result in less than optimal effectiveness based on our current understanding of the pathogenesis of hair loss. A number of factors including genetics, hormones, stress, and environmental exposure can trigger and sustain hair loss pathophysiology.[18] These factors may interact and influence each other significantly impacting follicular biology. As dermatologists we characterize hair loss based on morphology and etiology, scarring vs. non-scarring, hereditary vs. acquired, and inflammatory vs. non-inflammatory. But recent studies suggest there may be more similarities than differences across the hair loss spectrum. Micro-inflammation at the level of the follicle is a common thread in all types hair loss including androgenetic alopecia.[18,19,20,21,20,22] Factors such as ultraviolet light, pollution, toxins, smoking, antigenic exposure to bacteria and fungi, emotional stress, and androgens promote a pro-oxidant and pro-inflammatory environment in the follicle.[22] Although not immediately destructive, over time this can dysregulate the signaling pathways known as the intrinsic regulators of hair follicle stem cell homeostasis and hair follicle cycling.[19-22] Reactive oxygen species trigger the release of pro-inflammatory cytokines such as IL-1 and TNF-α, and the pro-fibrotic and growth-inhibiting TGF-b. These cytokines promote apoptosis and cause follicular regression, premature termination of the anagen phase, and miniaturization. To this end, any therapies designed to treat hair loss must be multi-targeting, geared to address not only triggering factors but mitigate downstream mediators of inflammation as well.

The Use of Botanicals for Treating Hair Loss

The use of botanicals for medicinal purposes is the practice of phytomedicine. Although technically considered complementary and alternative medicine, botanicals have now become mainstream and are used in all fields of medicine. In dermatology, phytoactives are currently used for photoprotection, chemoprevention, and to treat conditions such as polymorphous light eruption, psoriasis, eczema, melasma, and vitiligo.[23-25] The next logical application of botanicals is for the treatment of hair loss because of their multi-modal biologic activity against its causative factors including: inflammation, DHT, stress mediators, oxidative damage, and intermediary signaling cascades. Furthermore, there are safe, solvent-free technologies available today for extracting the most potent phytoactive plant parts and standardizing them to exact doses that produce specific clinically studied effects. Advances in biotechnology have also made way for bio-optimizing phytocompounds to improve absorption and bioavailability. The phytoactives discussed below have been selected based on their phytopharmacology and synergistic effects for treating hair loss (Figure 1). They are part of a patent pending Synergen Complex of highly purified, bio-optimized, standardized, and clinically tested extracts found in Nutrafol®, a novel dietary supplement (Table 1).

Curcumin: *Curcuma longa*

Curcumin is made from turmeric, the golden spice that is widely used for its flavor and color in Asian cuisine. In

FIGURE 1. Proposed synergetic mechanism of action of standardized nutraceutical ingredients against the triggers of hair loss.

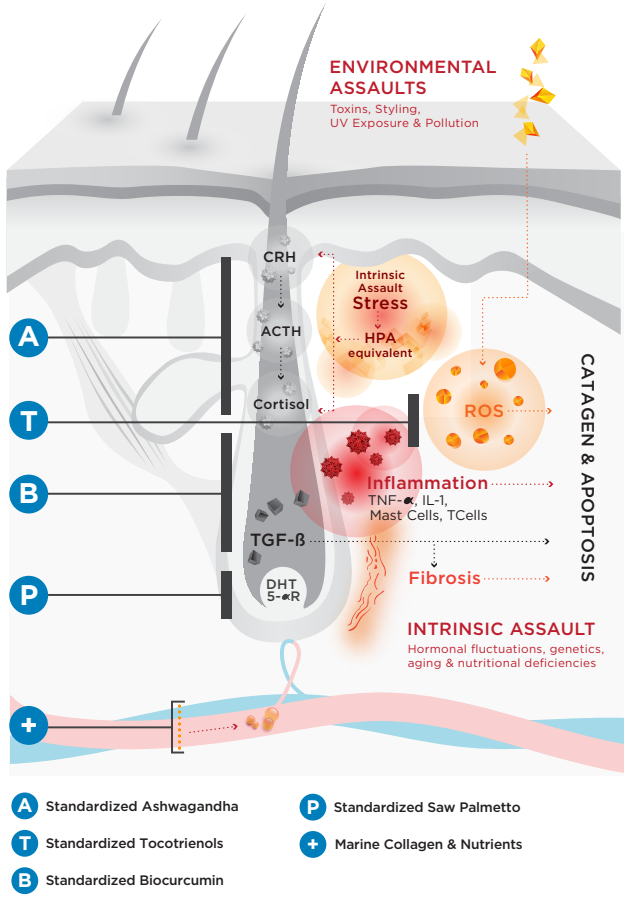


TABLE 1.

A Selection of Standardized Ingredients in Nutrafol	
Ingredient	**Standardized/bio-optimized**
Curcumin	BioCurcumin - Standardized to 95% curcuminoids
Ashwagandha	Standardized to 10% withanolides
Saw Palmetto	Standardized to >45% fatty acids and sterols
Tocotrienols/Tocopherols	Tocotrienol-rich, bio-optimized toctotrienol/tocopherol complex
Piperine	Bioperine standardized to 95% piperine
Marine Collagen	Hydrolyzed to 2kda for better absorption

*Nutrafol contains 21 ingredients in total.

Ayurvedic medicine, curcumin has been used for centuries to treat health conditions including respiratory illnesses, liver disease, and inflammatory disorders.[26] Curcumin is a highly pleiotropic molecule that modulates the activity of enzymes, growth factors, and numerous signaling pathways.[27] As such, curcumin has a diverse pharmacologic profile functioning as an anti-inflammatory, antioxidant, anti-carcinogenic, anti-diabetic, anti-coagulant, anti-microbial, hepatoprotective, and cardio-protective agent with additional anti-aging properties.

Curcumin is most recognized as a potent anti-inflammatory and immunomodulator,[28] and as such it provides a potential option to counter the inflammatory component of hair loss, without the usual side effects of most anti-inflammatory and immunomodulatory drugs. Curcumin down-regulates inflammatory pathways including cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthatase (iNOS) enzymes. Curcumin inhibits transcription factor NF-kB decreasing the pro-apoptotic inflammatory cytokines TNF-α and interleukin 1 that cause follicular regression. In addition to functioning as an anti-inflammatory, curcumin has broad antioxidant activity. It is a dual antioxidant meaning it is a scavenger of free radicals and capable of boosting endogenous antioxidant levels. Curcumin up-regulates transcription factor nuclear factor erythroid-like-2 (Nrf-2).[29] Nrf-2 increases the synthesis of enzymatic antioxidants such as hemoxygenase 1 and glutathione increasing cellular antioxidant defense.

Curcumin was also shown to be a naturally occurring anti-androgen.[30-32] Studies on prostate cancer cell lines demonstrate that curcumin inhibits aberrant androgen receptor (AR) expression.[30,31] The AR plays an important role in the control of hair growth and is also overexpressed in follicles affected by androgenetic alopecia. In vitro models of androgenic alopecia have also shown isolates of turmeric and curcumin to have effects against 5-a reductase (5-aR) [32] supported by clinical data from topical studies.[33,34] Perhaps the most interesting and valuable effect of curcumin in the androgen pathway is its demonstrated capacity to stabilize aberrant androgen-induced downstream TGF-b signaling that in follicles induces catagen, hair growth inhibition, and perifollicular fibrosis.[27,31,35]

Stress-induced perifollicular mast cell activation and degranulation plays a key role in stress-triggered inflammatory events in hair loss via the cytokines and mediators released.[36] Mast cell stabilization seems to be a promising approach to skin conditions induced and aggravated by stress, but little is available pharmacologically.[36,37] Evidence shows that curcumin is a natural mast cell stabilizer, and was recently shown to inhibit Substance P-triggered activation and degranulation of connective tissue type mast cells - suggesting its potential use for stress-induced neurogenic inflammation.[38,39] Further, curcumin was shown to decrease levels of SP in animal stress/pain models, and in a recent human study this correlated locally with decreased skin itching.[40,41]

Although the biologic activity of curcumin is well defined, its use is limited by poor absorption and rapid metabolism resulting in limited bioavailability[42]. The amount that is absorbed is converted to dihydrocurcumin and tetrahydrocurcumin that are further converted to monoglucuronide conjugates in the liver and intestines.[43] Studies have demonstrated that co-administration of curcumin and the botanical piperine, found in black pepper (Piper nigrum) and long pepper (Piper longa), increases the bioavailability of curcumin. Piperine inhibits the enzyme responsible for glucuronidation and can increase plasma levels up to 154% after ingestion of high dose curcumin (2000mg/kg).[44] A novel approach for increasing bioavailability of curcumin is to standardize it to higher percentage curcuminoids and to reconstitute it with non-curcuminoid oil components of turmeric.[45] In a comparative study, a patented formulation (BCM-95®CG) containing 95% standardized curcumin and non-curcuminoid components was found to have approximately 700% better absorption than curcumin alone or a curcumin-lecithin-piperine formulation.[45] Human clinical trials supplementing with this formulation have shown curcumin to significantly reduce inflammatory biomarkers like CRP and ESR.[27,46]

Ashwaghandha: *Withania somnifera*

Ashwaghandha, also known as Indian Ginseng or Wild Cherry, is a botanical with a broad range of biologic effects. It has been used for centuries in Ayuvedic medicine to bring the body in balance, build energy and resistance to stress.[47] Valued for these properties, ashwaghandha is considered an adaptogen: a group of botanicals that when taken daily leads to homeostasis, stabilization, and a greater ability to resist and recover from stress. Elevated stress and cortisol levels have been recently shown

to play a pivotal role in hair loss pathology.[37] Ashwaghanda contains biochemical constituents including steroidal lactones (withanolides), sitoindosides, and other alkaloids.[48] Withanolides interact with various signaling pathways, transcription factors such as NFK-b, and heat shock proteins that interact with steroid receptors. Withanolides anti-stress properties are attributed to their ability to mimic certain corticosteroids, interact with steroid receptors and modulate and reduce cortisol levels, thereby modulating the stress response.[49-51] In a double-blind placebo-controlled study, daily supplementation with standardized 10% withanolide ashwaghanda in patients with a history of chronic stress resulted in a significant reduction in stress scales and lowering of elevated serum cortisol levels as compared to controls.[49]

Withanolides also increase endogenous antioxidants, decrease inflammation, modulate immune response, and prevent carcinogenesis.[52] Ashwaghandha increases cell mediated immunity by increasing nitric oxide levels in macrophages, thereby enhancing phagocytic capability.[53] The effects of standardized withanolides on inducing endothelial nitric oxide synthase also help improve blood flow, which may increase oxygenation and nutrient delivery to the follicle.[54]

Saw Palmetto: *Serona repens*

Saw palmetto extract (SPE) is a botanical that has been evaluated for treating benign prostate hyperplasia (BPH) and associated erectile dysfunction.[55] Saw palmetto extract is a natural inhibitor of both isoforms of 5-alpha reductase, preventing conversion of testosterone to the active form DHT.[56] Although there is conflicting data surrounding the use of SPE for treating symptoms of BPH, it remains of interest as a natural active for treating androgenetic alopecia.[57] In a 2014 comparative study, 100 men with mild to moderate AGA were treated with 320mg of saw palmetto or 1mg finasteride daily for two years.[58] Global photographs before and after two years showed significant improvement in 38% of patients taking saw palmetto and 68% of patients taking finasteride. Although saw palmetto was more effective in the vertex area, a significant percentage in this group had stabilization or improvement in non-vertex areas as well. As expected, patients with more severe AGA responded more favorably to the pharmaceutical preparation. While finasteride's efficacy is confirmed by these studies, adverse events including erectile dysfunction are of concern. The use of saw palmetto to inhibit DHT may offer significant advantages in this regard. Animal studies suggest that saw palmetto may have potential for treating erectile dysfunction by increasing inducible nitric oxide synthase (iNOS) and acting as an inhibitor of phosphodiesterase 5 activity.[59] Further studies are warranted to determine the significance of these findings in the clinical setting. Additionally, saw palmetto has no effect of prostate specific antigen (PSA) levels, while they are significantly reduced in patients taking finasteride.[60]

Tocotrienols/Tocopherols

The vitamin E family consists of four tocopherols and four tocotrienols.[61] These eight lipid soluble vitamins are natural antioxidant compounds that are extracted from vegetable oils such as palm oil, rice bran oil, and oils derived from nuts, seeds, and grains. Vitamin E isoforms scavenge lipid peroxyl radicals preventing lipid peroxidation of cell walls.[62] Tocotrienols have superior lipid solubility compared to tocopherols and are far superior at preventing lipid peroxidation.[63] Patients with alopecia have been shown to have lower levels of antioxidants such as GSH and GSH-Px and an increase in thiobarbituric acid reactive substances (TBARS) that are indicative of lipid peroxidation[64]. Thus oral administration of antioxidants such as tocopherols and tocotrienols may be of value for mitigating oxidative stress and lipid peroxidation.

In a randomized, placebo-controlled study, supplementation with a standardized tocotrienol-rich tocotrienol-tocopherol complex was evaluated on 38 patients with hair loss ages 18-59. Patients in the tocotrienol group showed a gradual mean increase in hair counts from a pre-determined scalp area from baseline with a mean increase of more than 34% by the end of the study. The placebo group showed no appreciable increase in hair counts. Cumulative weight of 20 strands of hair was not different between baseline and 8 months in either the supplement and placebo group after 8 months.[65] The authors suggest that the observed effect was most likely due to the antioxidant activity of tocotrienols, inhibition of lipid peroxidation, and oxidative stress in the scalp.[65,66]

Black Pepper Fruit: *Piperine*

The concept of enhancing bioavailability using natural compounds is gaining favor as method of drug delivery.[67] Referred to as *natural bioenchancers*, these compounds may act by decreasing hydrochloric acid excretion, increasing gastrointestinal blood supply, lengthening GI transit time, gastric emptying time, and gastrointestinal motility.[67] Additionally, natural bioenchancers can suppress first pass metabolisms and enzymatic breakdown. The first natural bioenhancer to be identified and studied extensively is piperine. As previously discussed, piperine inhibits glucuronidation of curcumin increasing bioavailablity.[44] Piperine also binds to vanilloid receptors in the gastrointestinal tract[68] activating membrane-bound adenyl cyclase, which catalyzes the synthesis of the second messenger molecule cAMP. cAMP activates protein kinase A (PKA) that inhibits intestinal motility and dilates blood vessels in the intestine.[69] This physiologic action of piperine results in better digestion and absorption of a variety of nutrients including herbal extracts, water and fat-soluble vitamins, antioxidants, and amino acids like lysine and methionine. Minerals such as zinc and selenium are also better absorbed when administered with piperine.[70]

FIGURE 2. 52-year-old woman at (A) one month and (B) seven months of treatment.

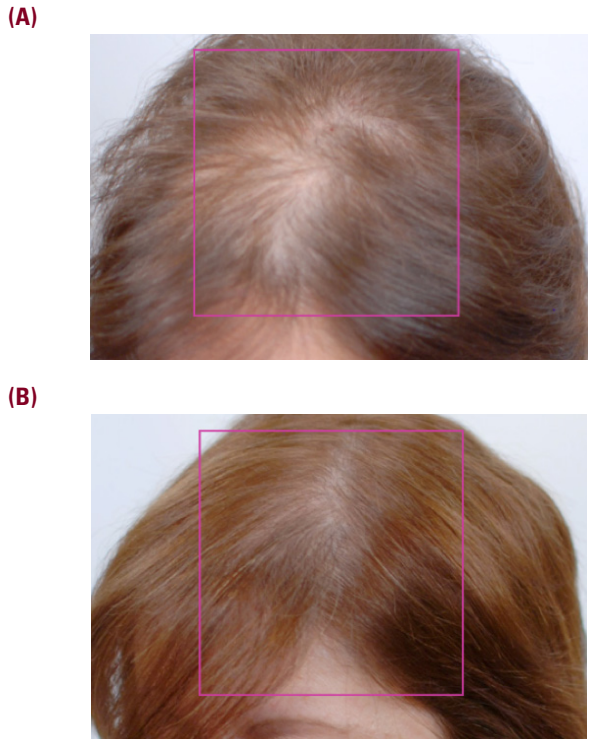
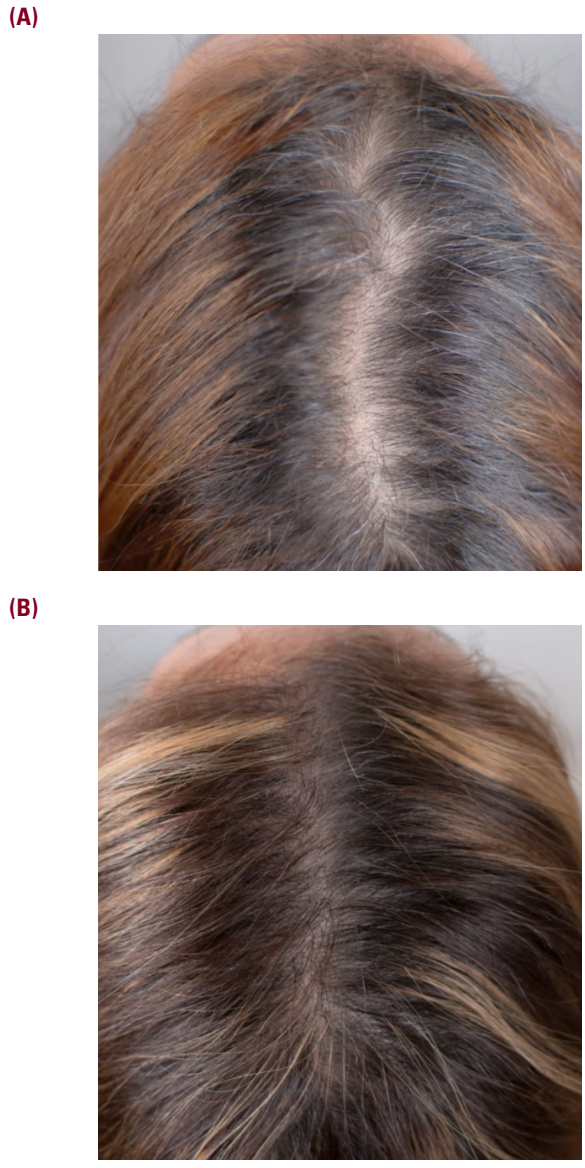


FIGURE 3. 45-year-old woman (A) before and (B) at four months of treatment.



Marine Based Ingredients (Collagen Hydrolysates)

Collagen is an essential component of the extracellular matrix.[71] Collagen hydrolysates are commonly extracted from marine sources for use in nutraceuticals. Hydrolyzing collagen yields dipeptides, tripeptides, and free amino acids. Following ingestion, radiolabeled collagen hydrolysates are absorbed in the intestines, distributed to tissues including the skin and persist for up to 14 days.[72] Collagen fragments serve as building blocks for collagen and bind to receptors on fibroblasts stimulating collagen production.[73] They also have antioxidant, photoprotective, and immune modulating properties.[74,75] Nutraceuticals containing collagen hydrolysates have been shown to improve hair growth in patients with telogen effluvium and androgenetic alopecia.[76,77]

Evaluation of Nutrafol® Safety and Efficacy

The hair loss supplement Nutrafol® is currently being investigated in several multi-center, randomized, double-blind, placebo-control studies . Herein we present several case studies of subjects treated with Nutrafol® as monotherapy. These cases demonstrate clinical improvement, and were associated with a high degree of patient satisfaction and a favorable safety profile.

Case 1

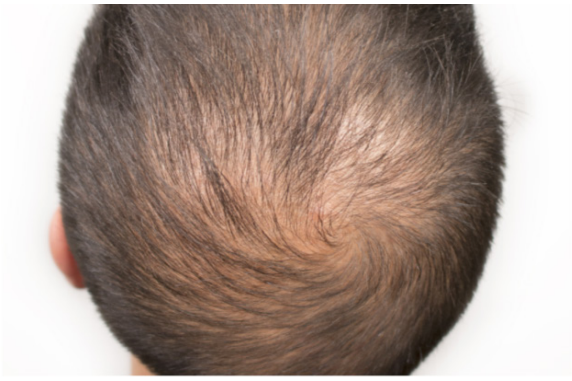
A 52-year-old woman before and after two years of Nutrafol® use (Figure 2). She had a history of chronic anemia, now resolved, and diverticulitis. She takes no medications. Her family history includes early hair loss in father, sister, and brother and she believes stress and childbearing triggered her hair loss. Prior to Nutrafol®, she tried minoxidil for a couple of months but discontinued after not seeing results. She expressed high levels of satisfaction with Nutrafol®, no side effects, and plans in continuing therapy indefinitely.

Case 2

A 45-year-old female with early signs of diffuse pattern hair loss before and 4 months after Nutrafol® supplementation (Figure 3). She had no family history of hair loss, did not want to take any prescription drugs and was seeking a nutraceutical solution

FIGURE 4. 37-year-old man (A) before and (B) at four months of treatment.

(A)



(B)

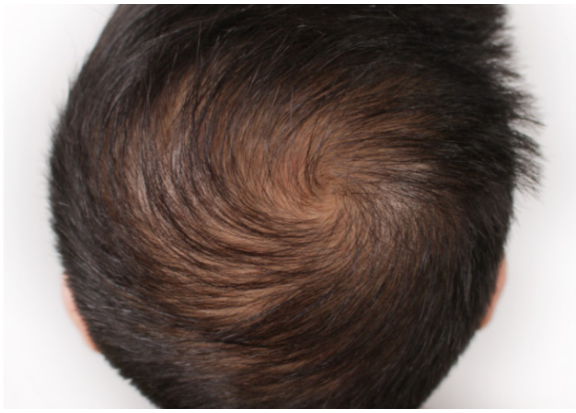
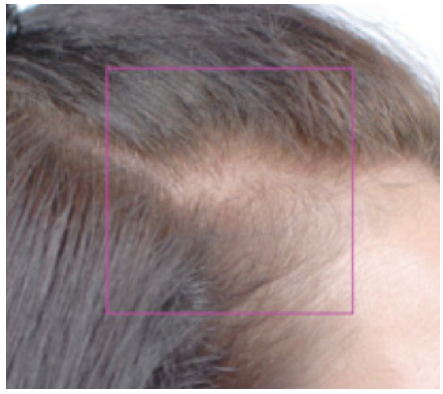
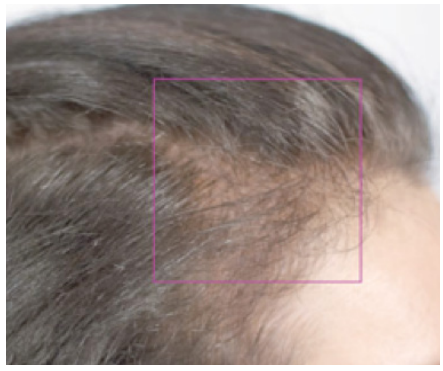


FIGURE 4. 38-year-old woman (A) before and (B) at three months of treatment.

(A)



(B)



for hair loss. She has expressed high level of satisfaction, no treatment side effects and plans to continue taking Nutrafol® as a preventative measure.

Case 3

A 37-year-old man with early male pattern hair loss, before and 5 months after daily Nutrafol® use (Figure 4). He has a strong family history of hair loss, and had previously tried minoxidil but ceased secondary to difficulty of use and cosmetic considerations. He did not want to start finasteride for fear of sexual side effects. He is satisfied with Nutrafol® effects on hair growth and shedding and plans to continue taking it indefinitely as a preventative with the prospect of adding PRP and LLLT therapy.

Case 4

A 38-year-old female with early diffuse thinning, predominantly in the temple area, before and after 3 months of daily Nutrafol use (Figure 5). She is healthy, with no medical issues and takes no medications. There is no family history of hair loss. The patient noticed thinning and increased shedding about 5 years prior and has taken biotin and other supplements in the past with no improvement. She reported several stressful life events and chronic stress during this time. She is satisfied with Nutrafol effects on hair growth, improvement in temple area coverage, as well as decreased shedding. She also reported improvement in experiential feelings of stress and anxiety. The patient had no treatment side effects and plans to continue therapy indefinitely.

CONCLUSION

Hair loss remains a challenge for patients and dermatologists alike. This multifaceted condition requires provider time, understanding and knowledge as there are multiple triggers and down-stream pathways involved in the pathogenesis. The use of botanicals and other natural ingredients appeals to patients who are looking for safe and effective treatments for hair loss. This article highlights some of the most important botanicals having pharmacologic effects that can mitigate triggers for hair loss and restore balance to the follicle. While there is no magic bullet or single natural ingredient to address all of the mechanisms at play in the multiple forms of clinical hair loss, by using the combination of bioactives described here, Nutrafol® offers a promising approach for hair loss patients.

DISCLOSURES

Dr. Farris is an advisor for Nutrafol and Nutraceutical Wellness Inc. Dr. Rogers and Dr. McMichael have no conflicts.

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