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Real-World, Open-Label Study of the Efficacy and Safety of a Novel Serum in Androgenetic Alopecia

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ABSTRACT

Pattern-type hair loss is a highly prevalent condition affecting the majority of men and women at some point in their lifetime. Although genetics and androgens are instrumental in the pathogenesis of this type of hair loss, it is increasingly recognized that inflammation, stress, and environmental factors play a central role. The few and widely used monotherapies approved by the US Food and Drug Administration, such as minoxidil or finasteride, are not efficacious in all people and cause adverse events that prevent patient compliance. Therefore, new treatments that are easy to use and that holistically address the multi-factorial pathophysiology of pattern-type hair loss are needed. Clinical studies have already demonstrated the safety and efficacy of a plethora of bioactive natural products, such as epigallocatechin gallate (EGCG), *Vitis vinifera* seed extract, *Glycyrrhiza* root extract, apigenin, and saw palmetto extract to name a few, in improving hair follicle homeostasis via anti-inflammatory, anti-androgen, anti-microbial, and anti-oxidant action. Here, we present a novel topical serum, REVIVV®, that contains a proprietary blend of phytochemicals designed to stimulate hair growth, reduce shedding, and restore homeostasis to the hair follicle. The serum's safety and efficacy were assessed in 150 participants in a real-world clinical setting. Findings demonstrate that twice-daily use of the serum significantly improves hair growth, and reduces shedding after 8 weeks of use. All participants rated the serum as easy to use and stated plans for continued use. Overall, the topical serum REVIVV® showed evidence of good efficacy related to hair growth and had positive cosmetic properties warranting further evaluation in clinical studies.

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INTRODUCTION

Androgenetic alopecia (AGA), the most frequent form of alopecia in men and women, is characterized by progressive hair loss in a pattern distribution over the galea aponeurotica of the scalp. Signs of AGA start at any time after puberty, due to increased androgen levels. By the age of 70, 80% of men and up to 40% of women are affected. While not considered a "disease" per se, hair loss can have detrimental consequences on the self-esteem and quality of life of affected individuals.[1,2]

According to the traditional view, the two most important factors in the etiology of AGA include genetic predisposition and androgens, leading to a patterned, non cicatricial alopecia in androgen-dependent areas of the scalp. The past few years, however, have seen a paradigm shift of thought on the nature of AGA, which is now recognized as a multifactorial disorder caused by a complex interplay between the epigenome, androgen metabolism, and 'nurture'.

Numerous histological, ultrastructural, and immunohistochemical studies have shown that miniaturization of hair follicles in AGA is accompanied by microscopic follicular inflammation and fibrosis, pointing to the central role of "micro-inflammation," a subtle indolent inflammatory process in pattern-type hair loss progression.[3-6] This chronic micro-inflammatory state is reinforced by internal and environmental stressors. For example, sun damage leading to photoactivation of porphyrins produced by *Propionibacterium sp.* in the pilosebaceous duct can cause oxidative tissue damage as well as the production of radical oxygen species and the release of proinflammatory cytokines by keratinocytes.[7,8] Disruption of the microbiome in the scalp milieu can lead to overcolonization by *Malassezia sp.* or *Demodex*, which further advances the inflammatory response. Other downstream effects, such as activation of apoptotic programs, loss of stem cell differentiation, perturbed microvasculature of the dermal papilla, toxic metabolite accumulation, and nutrient deficiency, together reinforce the vicious cycle, resulting in ongoing hair loss.[9]

Despite the recognition that the cause of AGA is multifactorial, the only treatments approved by the US Food and Drug Administration for AGA are either the topical androgen-independent hair growth stimulator minoxidil (2% in females or 5% in males), or oral finasteride (1 mg/d) in males. Minoxidil's mechanism of action is not fully understood, but is believed to stimulate anagen entry and promote nutrient and oxygen delivery to hair follicles, thereby shortening the telogen phase.[10] Finasteride is an anti-androgen that inhibits the conversion of testosterone to the more potent androgen, DHT. Both drugs can curtail progressive hair loss and stimulate new hair growth, but their efficacies are inconsistent across the patient population and limited in mechanistic scope; novel treatments that are either more effective or that are complementary to other lines of therapy are needed for the treatment of AGA. Alternative therapies, such as new generation nutraceuticals, energy-based devices, and regenerative treatments such as platelet-rich plasma (PRP), have been evaluated and show promise in promoting hair growth, but the need for new, safe, easy-to-use, and effective agents has not yet been adequately met.

TABLE 1.

Ingredients in REVIVV®	
Ingredient	**Mechanism**
Larix europaaea wood extract (taxifolin, DHQG)	Potent anti-inflammatory
Zinc chloride	inhibits *Malassezia furfur*
Camellia sinensis Leaf Extrac (epigallocatechin gallate, EGCG)	Sa-reductase inhibitor
Alanine/Histidine/Lysine Polypeptide Copper HCl	peptides complex, signals for cell rejuvenation in the dermis, ie, restructuring the dermis including hair follicles
Betaine	detoxifies homocysteine
Caffeine	phosphodiesterase inhibitor, leading to vascular dilation
Aesculus hippocastanum (Horse Chestnut) seed extract	anti-inflammatory and vascularization
Sodium hyaluronate	rebuilds the subdermal extra cellular matrix
Eriobotrya japonica (Loquat) leaf extract	Shown to stimulate FGF-7, VEGF, BMP-2 which promotes hair growth and suppresses FGF-5, induces hair loss and increases blood circulation
Glycyrrhiza uralensis (Licorice) root extract	prenylated isoflavones, potent antimicrobial
Phellinus linteus (mushroom) extract	β-glucan and terpenes, anti-inflammatory, promotes keratinocyte growth and proliferation
Houttuynia cordata extract	possible mechanism is local glucose modulation
Vitis vinifera (Grape) seed extract	procyanidins such as B2 and B3, promote anagen hair growth by reducing PKC isozymes and TGF-beta signaling
Aronia arbutifolia Extract	rich in antioxidant polyphenols
Malus domestica (apple) fruit extract	procyanidin B2 reduces PKC isozymes that signal for telogen
Wine extract	flavan-3-ols, potent antioxidants
Perilla frutescens leaf extract	rosmarinic acid, antioxidant, Sa-reductase inhibitor
Apigenin	anti-inflammatory
Oleanolic Acid	anti-inflammatory
Palmitoyl tripeptide-1	GHK with fatty acid ester, fat soluble peptide for rejuvenation
Biotinoyl tripeptide-1	GHK with biotin ester, bioavailable peptide for rejuvenation
Copper peptide-1	Cu-GHK, signals for rejuvenation
Glycogen	hair follicle food source
For Men	
Serenoa serrulata (S*aw palmetto*) fruit extract	contains sterols that inhibit 5α-reductase
For Women	
Soy isoflavones (*Glycine max*)	modulate gene expression associated with local metabolism
Sorbitol	hydrating
Pterocarpus marsupium bark extract	Epicatechin, flavonol C-glucosides, assists glucose metabolism
Glutamic acid	nutrient for protein, ie, keratin

A successful treatment for AGA needs to consider the multifactorial nature of the condition to address the wide array of targets via a combination of bioactive ingredients.[3,11] Aside from the right combination, homogenous product delivery and effective transepidermal passage of active ingredients need to be ensured. A selection of bioactive plant extracts and their isolates are known to possess pleiotropic anti-inflammatory, antioxidant, antimicrobial, and anti-androgen activities. The positive outcome from topical application of select extracts and isolates can therefore improve the physiology of hair follicles and scalp skin by modulation of proinflammatory cytokines, improvement of redox balance in cells, and a decrease of local steroidogenesis (DHT and cortisol formation). To this effect, a novel serum (REVIVV®) containing a proprietary blend of selected plant extracts and bioactives has been designed for the treatment of AGA (Table 1).

The blend utilizes a tea leaf extract (*Camelia sinensis*), one of the most extensively studied botanicals due to its antioxidant, anti-apoptotic, anti-androgen, and anti-inflammatory properties, originating from constituent catechins, 50% to 80% of which consist of epigallocatechin gallate (EGCG)[12,13] *Vitis vinifera* seed extract is also rich in bioactive products capable of enacting antioxidant and anti-inflammatory effects. These are flavonoids, polyphenols, transresveratrol, and procyanidins, such as procyanidin B2. Proanthocyanidins have been demonstrated through in vivo studies to promote anagen entry.[14,15]The REVIVV™ proprietary blend also includes an extract from the wood of European Larch (*Larix europaea*), which is rich in the flavanone taxifolin, a potent antioxidant that scavenges toxins and free radicals from the hair follicles and surrounding area.

To counteract microbial accumulation derived from glucose imbalance and lipid accumulation, natural ingredients that antagonize Gram-positive bacteria and fungi, such as the prenylated isoflavones in licorice (*Glycyrrhiza uralensis*), zinc chloride, and hexamidine diisethionate, are incorporated into the formula. *Glycyrrhiza uralensis* also contains glycosides, terpenoids, phenolics, and flavonoids, which have anti-androgen and immunomodulatory action. In a study comparing 2% minoxidil with 2% extract from *G. uralensis*, the latter showed superior efficacy in hair growth promotion. Horse chestnut (*Aesculus hippocastanum*), which is a powerful anti-inflammatory,[16] together with caffeine, helps regulate dermal vasculature and oxygen supply to the hair follicles.[17] Caffeine has been extensively utilized in topical formulations designed to promote hair growth. Aside from its anti-inflammatory and anti-androgen properties, caffeine can penetrate efficiently via the follicular route. Studies have shown that 2 minutes is sufficient for a caffeine-containing formula to penetrate deeply into the hair follicles, and it can remain there for up to 48 hours, even after hair washing.[18] REVIVV® also contains a complex mixture of tripeptides with unique penetrating abilities, such as biotinyl tripeptide-1, triterpene oleanolic acid, and flavanone apigenin. These products rejuvenate the hair follicles by dampening inflammation, restoring cellular metabolism, and inhibiting androgens.[19]

Other ingredients in the formula that support scalp health and facilitate ingredient penetration are sodium hyaluronate, menthol, and mentha piperita oil.[20] REVIVV™ is customized for both genders. The men's formula includes saw palmetto (*Serenoa serrulata*), which has anti-androgen properties, while the women's formula includes isoflavones, sorbitol, glutamic acid, and the extract of *Pterocarpus marsupium*.

The present study aimed to evaluate the efficacy and safety of twice-daily application of REVIVV® serum in the treatment of AGA in a real-world setting. In addition, patient satisfaction with the treatment and the product's cosmetic attributes was evaluated.

MATERIALS AND METHODS

Study Design

This was an open-label, prospective, observational, real-world study conducted in one center in New Jersey (Cosmetic Skin) from January 2022 to June 2022. The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonization and Good Clinical Practice guidelines as applicable to cosmetic products. All subjects provided written, informed consent to use their information in the current study, including photography, and each received their patient information subsequent to the study.

Patients

Enrolled subjects were male and female adults aged 18 to 75 years of age with a diagnosis of AGA. Clinical severity ranged from mild to severe. Subjects with evidence of hair loss for reasons other than AGA were excluded. Use of oral or topical hair growth products was not permitted in the 4 weeks preceding the study and during the study. During the study, participants were instructed to not use any hair treatments that could affect hair loss, and not to change their usual hair hygiene habits, diet, exercise routine, or contraceptive method. Anti-inflammatories, antihistamines, immunosuppressive therapies, and retinoids were prohibited during the study.

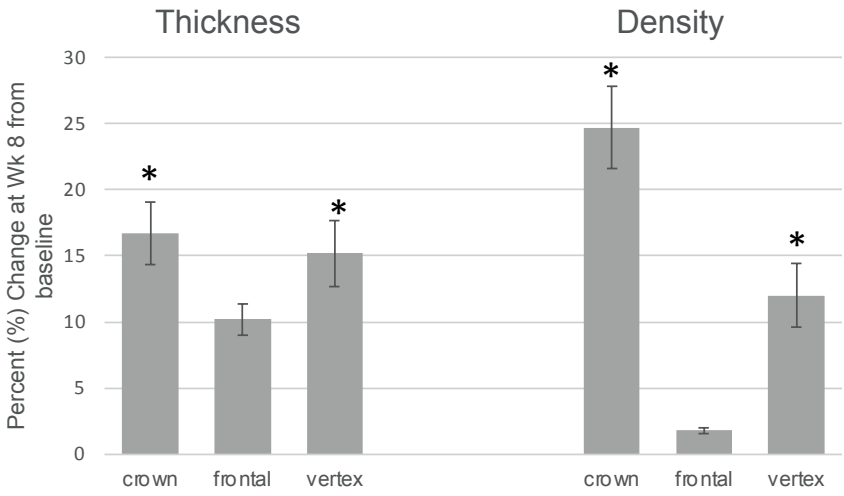
Treatment

Participants applied the product (drug free REVIVV®) at home, in accordance with the product's instructions for use: the roller was massaged in circular motions all over the frontal, crown, and vertex areas of the scalp. The product was applied twice per day and left on overnight.

Assessments

Adverse events were monitored throughout the study. A

FIGURE 1. Change in thickness and hair density at week 8 from baseline as measured by trichograms in the frontal, crown, and vertex area of the scalp. Asterisk denotes statistical significance ($P<0.05$).



dermatologist assessed for erythema, edema, vesicles, papules, macules, crust, dryness, and dyschromia, and participants were questioned at follow-up (8 weeks after baseline) about any feelings of discomfort, such as burning or stinging. Efficacy assessments included digital phototrichogram for a subset of patients, digital photography, and patient questionnaires. For the phototrichogram assessment, images were taken using the computerized trichogram Tricho Scan (Dermoscan GmbH, Regensburg, Germany), and changes in hair shaft thickness and hair density (hairs per centimeter squared) were calculated at week 8 from baseline. Statistical analysis was performed with a paired t-test to compare the before and after data for each parameter measured on trichogram. Patient questionnaires were completed 8 weeks after treatment initiation. Participants assessed the product's effects and cosmetic qualities via a 5-point Likert scale (greatly improved, slightly improved, no change, slightly worsened, greatly worsened), and yes/no questions on satisfaction: whether it's easy to use, whether it affects the hair styling, and whether they will continue using the product.

RESULTS

Out of the 150 subjects that were enrolled in the study, compliance was 100%. Baseline characteristics of patients are shown in Table 2: mean age was 56.4 years, and 60% of participants were female. None of the participants reported discomfort and no adverse reactions were detected on examination.

Seven patients participated in the phototrichogram substudy. Phototrichogram analysis showed a statistically significant increase in hair thickness in both scalp areas (crown, vertex) at week 8 from baseline (Figure 1). Representative images from a male and female patient with AGA after 8 weeks of REVIVV® are shown in Figure 2.

FIGURE 2. 47-year old female (A) and 65-year old male (B) patients before and after the 8-week follow-up after twice-daily use of REVIVV®

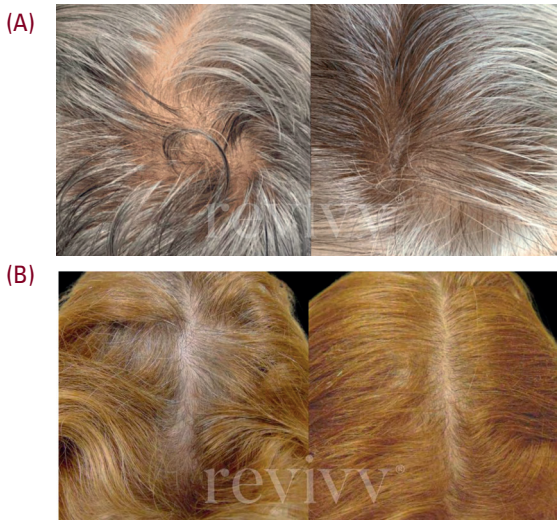
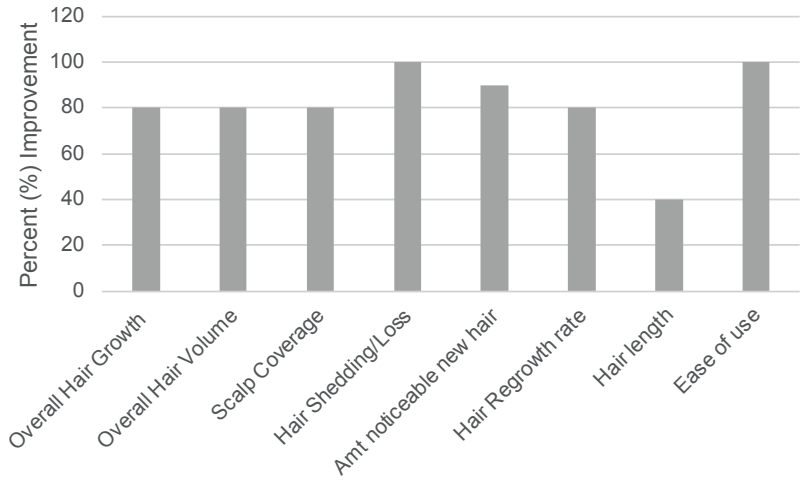


TABLE 2.

Subject Baseline Characteristics	
Parameter	
Average age	
(range) years	56.4 (38-75)
Female %	60%
Skin Type	
I	10%
II	20%
III	40%
IV	10%
V	15%
VI	5%

FIGURE 3. Results of patient satisfaction questionnaires in regard to REVIVV® efficacy and cosmetic properties.



On the participant questionnaire, the product was rated highly, both for efficacy and cosmetic qualities. At week 8, 80% of participants independently observed an increase in hair growth, hair volume, scalp coverage, and amount of hair regrowth. Ninety percent of participants noticed an increased frequency of new hair while all participants said the hair shedding decreased and the product was easy to use (Figure 3). Cosmetically, the product was rated very highly: all patients said the product was easy to use, did not affect styling, and most patients would continue to use it.

DISCUSSION

The use of the novel topical serum REVIVV® improved hair growth in the current study of 150 participants in a real-world clinical setting, as demonstrated by both clinical corroboration and subjective patient self-assessment. Analysis of phototricograms at week 8 (post twice-daily use of the topic serum) revealed a significant increase in hair thickness and hair density in the vertex and crown areas of the scalp. Moreover, almost all participants found the product to be effective, easy to use, and easy to incorporate into their hair routine, and said they would continue using it.

In the current paradigm, hair loss is regarded as a multifactorial condition, etiologically derived from genetics (or epigenetics), androgen imbalance, environmental exposure, medications, nutrition, and intrinsic aging, all contributing to its progression. Treatments need to be designed accordingly, not as monotherapies but rather with the goal of formulating a multi-prong approach, targeting all the etiological factors to stop and reverse AGA, then restore hair follicle homeostasis. Topical drug-free cosmetics, such as REVIVV®, can provide a safe alternative or adjuvant to systemic drug treatment, reducing the potential side effects. The key to successful treatment is finding the most effective combination of bioactives that have additive or synergistic mechanisms of action, achieve appropriate penetration and fast results.

As described extensively in the introduction, existing scientific literature demonstrates efficacy for a number of phytochemical products in ameliorating AGA, and in some cases, their mechanism of action is explored or explained. The results of the current study agree with several in vitro and in vivo studies and add to this body of literature. The green tea extract that is rich in polyphenols mitigates inflammatory activation pathways, enhances stem cell proliferation, and directly or indirectly modulates metabolic processes occurring in the cells of the hair follicle. Extracts rich in flavonoids, such as *V. vinifera*, *L. europaaea*, and *Malus domestica*, stimulate and ameliorate the pathologic barriers to the anagen phase of the hair follicle and decrease apoptosis by protecting against oxidative stress and follicular cell senescence. The formulation also includes ingredients that enhance absorption of other ingredients (ie, menthol and caffeine), those that promote rapid absorption, and tripeptides that are modified for efficient transdermal passage into the dermis and hair follicle. Although the multi-modal composition creates an umbrella of therapeutic effects that are applicable for both male and female androgenetic alopecia, the composition is tailored to either gender as a men's and women's formula to shift emphasis in favor of minimal differences in pathogenesis. For men the ingredients are enriched in anti-androgens; whereas, in women, the antioxidant ingredients have been doubled.

Aside from efficacy, the cosmetic properties of topical hair growth serums should not negatively alter existing hair, and should be conducive to a variety of hair care routines to promote regular use. The results of this study, which was conducted with

ethnically diverse participants, showed a high level of subject satisfaction with both the hair growth benefits and the cosmetic properties of REVIVV®. There were no reports of skin irritation, or dermatitis that sometimes occurs with the use of botanicals.

Limitations of this study are the lack of a placebo group, small sample size, and a short time of intervention. Specifically, while trichograms showed significantly increased hair density and thickness in the vertex and crown region, results were not as impressive in the frontal region. This is likely due to the short follow-up (8 weeks), and a longer follow-up in this region where androgen activity is increased is warranted. Despite these limitations, we consider that this real-world study showed the product is promising in treating hair loss by addressing the complex pathophysiology associated with hair loss.

In conclusion, there is an increasing interest in alternative treatments for male and female pattern-type hair loss that are simple and cost-effective with no adverse effects for patients who are unsatisfied with conventional therapy. Diverse formulations are being developed to address this demand, but are limited by the high heterogeneity of ingredients and lack of peer-reviewed or real-world evidence. Here, we show that twice-daily use of the novel topical serum REVIVV® by 150 patients from an ethnically diverse real-world setting led to meaningful improvements in hair growth with high patient satisfaction and no side effects. Larger clinical studies with a longer follow-up to evaluate efficacy are currently underway.

DISCLOSURES

JR, NS, and NS are advisors of WeThrivv LLC, the provider of Revivv®. SA, AS, and ZA have no conflicts to disclose.

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