

SCIENTIFIC RATIONALE

Nicholas J. Sadgrove, PhD.
Scientific Advisor
VIAS Partners, LLC.
Doylestown, PA USA

INTRODUCTION

Hair loss and hair thinning is a challenge faced by both men and women. Although most of the research has focused on the male form of hair loss, it is becoming implicit that the causes of hair loss are very similar between men and women. For this reason, we no longer call it 'male pattern baldness' because this condition also afflicts women. In both sexes there is a strong androgenic driver, so it is called androgenetic alopecia (AGA) [1]. The slight differences between the two sexes also need to be recognized in therapeutic strategy, however, most ingredients are unisex.

Dihydrotestosterone, or DHT, is a steroidal androgen that is elevated in both male and female forms of AGA. In AGA, the 'spanner in the works' is the high level of DHT, because it interrupts or prevents harmonious metabolism of sugars and growth factors that normally nurture the growth of hair [2]. For this reason, blockers of the enzyme 5-alpha reductase have shown efficacy across both genders [3]. However, the havoc that is wreaked in the cutaneous tissues, that are the 'bed' for hair follicles, is not resolved by using monotherapy drugs that target 5-alpha reductase alone, such as pharmaceuticals that follow a 'top down' approach to hair therapy. To fully conquer the effects of DHT a multi-modal composition is necessary [1,4].

DHT changes the metabolism of sugar in the hair follicle. Consequently, the energy is used up and converted into fat, making the hair oily. Normally sugars are metabolized into an energy store called 'glycogen', that is the food source for anagen hair follicles [5], but with a high concentration of DHT it is converted to fat in an instant, generating more toxins in the scalp than normal, which creates oxidative damage to the tissues [6] and interferes with metabolism of other molecules, like cholesterol and vitamin A. Hence, therapeutic intervention requires targeting not just the formation of DHT, but also these bad 'downstream effects.'

Unfortunately, as the hair bulbs become oilier a bacterial overgrowth occurs in the hair passage, which causes the immune system to respond by triggering mild inflammation. In the published literature the accepted term to describe this mild inflammation is 'microinflammation' [1,3]. Thereafter, the bacteria secrete a signaling molecule (PPAR-gamma agonist) that tells the cells to keep making oil [7]. The inflamed oily scalp loses its ability to adequately circulate toxins off site, such as the toxins created in the conversion of sugar to fat. In the unhealthy scalp environment other enzymes start to fail, such as the cytochrome P450 aromatases that convert DHT into a beneficial hormone, and of course the cholesterol lowering enzymes mentioned previously [2].

REVIVV INGREDIENT RATIONALE: UNISEX INGREDIENTS (INGREDIENTS FOR MEN AND WOMEN)

The key to having a powerful hair growth serum is to target as many of the negative factors as possible in the first instance, by removing obstacles to hair growth, then to provide a boost to hair growth in the second instance, by signaling the hair follicles to come back to life. Hence, the unisex ingredients that give the power to our topical formulation are designed to confer an umbrella of effects, not just against DHT itself but also against its downstream effects, then finally to kick start the growth cycles of the hair shafts. How this is achieved is described in the following text.

To start with, the composition includes the REVIVV™ proprietary blend. This blend utilizes a tea extract (*Camelia sinensis*), which is rich in a polyphenol called epigallocatechin gallate (EGCG). This ingredient has been shown to have an antagonizing effect against 5-alpha reductase [8], the enzyme that converts testosterone to DHT. Then there is an extract from horse chestnut (*Aesculus hippocastanum*), which is a powerful anti-inflammatory [9], so it helps to resolve the 'microinflammation' mentioned previously. This extract is also a well-known therapy for circulatory problems [10], so it is likely that it improves the dermal vasculature and oxygen supply to the hair follicles. Improvement to vasculature will also facilitate the removal of toxins off site (from the scalp).

The REVIVV™ proprietary blend also includes an extract from the wood of European Larch (*Larix europaea*), which is rich in the flavonoid taxifolin, a potent antioxidant. This is important as the conversion of sugars to fats in AGA generates toxins, which are also known as reactive oxygen species or 'free radicals.' In this case, a powerful and penetrating antioxidant is necessary to remove the bottle neck in therapies. Taxifolin serves this purpose very well because in the process it is converted into a safe by-product. Finally, taxifolin complements the effects of horse chestnut by increasing the anti-inflammatory power of the formula [11].

At this point most of the negative factors have been antagonized. However, one of the remaining bottle-necks to the hair growth therapy is the microbial over growth in the hair shaft passage way. These Gram-negative bacteria, known as *Propionibacterium acnes*, continue to send signaling molecules to convert sugar to fat [12], taking part in what is known as the 'feedback loop' or 'vicious cycle' that was originally started by DHT. This bacterium works in collaboration with the fungus that causes dandruff in some people, called *Malassezia furfur*, which is another oil loving microbe. The orchestration of inflammation and oil production by these two microbes is defeated by using antimicrobial therapies. Hence, the 'WETHRIVE' formula includes natural ingredients that antagonize Gram-positive bacteria, such as the prenylated isoflavones in licorice (*Glycyrrhiza uralensis*) and the fungi are antagonized using zinc chloride. To reinforce the antimicrobial power of this blend, hexamidine diisethionate is also included.

By resolving these obstacles to hair growth, the foundation is returned to normal and the injured hair follicles are prevented from further injury, yet they continue to lay dormant or in a miniaturized state. To stimulate a return to normal growth the follicles are stimulated with caffeine, a molecule that has a similar effect as minoxidil (stimulating blood vessel dilation). Hair follicles are also signaled to rejuvenate by using a complex mixture of tripeptides that the system recognizes as a sign of tissue injury [13]. The reason for such a complex mixture is because each of the peptides has a unique penetrating ability, so each unique peptide reaches a different type of tissue and does its work there.

Lastly, there are several ingredients that improve the health of the dermis, such as sodium hyaluronate, which is a building block of the extracellular matrix. Menthol and *Mentha piperita* oil are penetration enhancers that increase the penetration of ingredients [14], such as the taxifolin and EGCG from tea. However, a more detailed breakdown of ingredients is given in the Table below.

Ingredient	Mechanism
<i>Larix europaea</i> wood extract (taxifolin, DHQG)	potent anti-inflammatory
Zinc chloride	inhibits <i>Malassezia furfur</i>
<i>Camellia sinensis</i> Leaf Extract (epigallocatechin gallate, EGCG)	5α-reductase inhibitor
Alanine/Histidine/Lysine Polypeptide Copper HCl	peptides complex, signals for cell rejuvenation in the dermis, i.e., restructuring the dermis including hair follicles
Betaine	detoxifies homocysteine
Caffeine	phosphodiesterase inhibitor, leading to vascular dilation
<i>Aesculus hippocastanum</i> (Horse Chestnut) seed extract	anti-inflammatory and vascularization
Sodium hyaluronate	rebuilds the subdermal extra cellular matrix
<i>Eriobotrya japonica</i> (Loquat) leaf extract	Shown to Stimulate FGF-7, VEGF, BMP-2 which promotes hair growth and suppress FGF-5, which induces hair loss and increases blood circulation
<i>Glycyrrhiza uralensis</i> (Licorice) root extract	prenylated isoflavones, potent antimicrobial
<i>Phellinus linteus</i> (mushroom) extract	β-glucan and terpenes, anti-inflammatory, promotes keratinocyte growth and proliferation
<i>Houttuynia cordata</i> extract	traditional medicine for hair, possible mechanism is local glucose modulation
<i>Vitis vinifera</i> (Grape) seed extract	procyanidins such as B2 and B3, promote anagen hair growth by reducing PKC isozymes and TGF-beta signaling
<i>Aronia arbutifolia</i> Extract	rich in antioxidant polyphenols
<i>Malus domestica</i> (apple) fruit extract	procyanidin B2 reduces PKC isozymes that signal for telogen
Wine extract	flavan-3-ols, potent antioxidants
<i>Perilla frutescens</i> leaf extract	rosmarinic acid, antioxidant, 5α-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

REVIVV INGREDIENT RATIONALE: INGREDIENTS TAILORED TO EITHER MEN OR WOMEN

The formula is tailored to either men or woman according to the specific needs of either sex. The men's formula includes saw palmetto (*Serenoa serrulata*) fruit extract, which strengthens the anti-DHT power of the formula, because men tend to have higher levels of DHT than women in cases of hair loss. The women's formula includes isoflavones, sorbitol, glutamic acid and extract of *Pterocarpus marsupium*. These ingredients antagonize the conversion of sugars to fats and provides targeted nutrients for hair fiber formation.

For men	
<i>Serenoa serrulata</i> (Saw palmetto) fruit extract	contains sterols that inhibit 5α-reductase
For women	
Soy isoflavones (<i>Glycine max</i>)	modulate gene expression associated with local metabolism
Sorbitol	hydrating
<i>Pterocarpus marsupium</i> bark extract	epicatechin and flavonol C-glucosides, assists with local glucose metabolism
Glutamic acid	nutrient for protein, i.e., keratin

SUMMARY

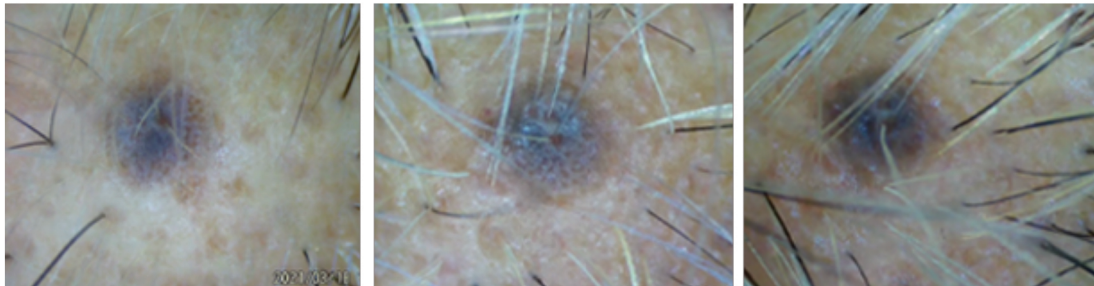
The challenged faced by those living with hair loss goes beyond the effects caused by DHT. This is because the changes to the metabolism in the hair follicle, as caused by DHT, create negative effects further down the biochemical cascade. Thus, it is important to address both DHT and its downstream effects by applying a multi-modal composition that creates an umbrella of therapeutic effects. Fortunately, there is a strong overlap between male and female androgenetic alopecia, so therapeutic ingredients are generally unisex. Importantly, resolving inflammation and quenching reactive oxygen species can strongly reverse the negative effects of too much DHT. The composition from WETHRIVV adequately covers this and delivers ingredients that antagonize the formation of DHT. The formulation also includes ingredients that enhance absorption of other ingredients, i.e., menthol is included to promote rapid absorption, and many of the polypeptides are modified for efficient passage to the various tissues in the skin layers and hair follicle.

The composition is tailored to either gender, as a men's and women's formula, to resolve the minute differences in pathogenesis. For men it is important to conquer the elevated DHT because this is more problematic in men, so the ingredients that inhibit the formation of DHT have been doubled. For women it is necessary to resolve the formation of reactive oxygen species and deliver nutrients that have become deficient, so the ingredients that resolve oxidative damage have been doubled. Nevertheless, the umbrella of unisex ingredients that are present in the male and female formula are more than adequate to address hair loss at interventional levels by antagonizing the bottleneck, then stimulating the hair follicles to return to life.

Figure 1. Global Image showing hair growth at 4 and 8 months following use of REVIVV(tm) topical serum twice daily.



Figure 2. Trichoscans showing hair growth at 4 and 8 months following use of REVIVV(tm) topical serum twice daily.



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