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New Insight Into the Multifactorial Pathophysiology of Hair Loss: Inflammation, Stress, and Follicle Biology Take Front Stage

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INTRODUCTION

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Journal of Drugs in Dermatology

A New Look at Pathogenesis of Hair Loss

Leon H. Kircik MD

Television and magazine commercials would have us believe that the secret to full, healthy hair is choosing the right shampoo or vitamin supplement. Drug store aisles are crammed with products that promise to improve the shine, texture, and/or thickness of hair with a variety of ingredients. Yet, we are aware that the biology of hair growth is complex and so, therefore, is the science of hair loss and hair care. While there are a number of products that can help healthy hair look healthier, shampoos or vitamins alone can't truly regrow thinning hair. As dermatology providers, we realize this not only because we know the science, but because we see patients in the clinic every day who ask us how they can help to reverse hair loss and improve the quality of their hair. Many of these patients are frustrated and sometimes distressed because "nothing helps" their thinning hair.

As our understanding of the microenvironment of the hair follicle deepens, it is becoming increasingly clear that targeting a single pathway in this complex system is not ideal. Androgens, cortisol, and corticotropin-releasing hormone, all of which are not in balance in hair loss due to internal and external stress, and gene expression of pro-inflammatory mediators all affect the hair follicle to suppress "normal" function and negatively influence hair growth. Extrinsic triggers, such as ultraviolet light, pollutants, tobacco, and a host of pathogens that are known to negatively affect the skin overall, also affect the hair follicle in the same way and they can stimulate an inflammatory response and/or lead to the release of reactive oxygen species (ROS).[1,2,3,4,5,6] We traditionally have divided hair loss into inflammatory vs noninflammatory, genetic vs acquired, hormone driven vs not. However, we are now realizing that a common inflammatory component is present in most hair loss pathogeneses including androgenetic alopecia (AGA).[7,8,9,10] Even though AGA has been known as a non-inflammatory type of hair loss, there is "micro-inflammation," presenting in perifollicular lymphocytic infiltrates, mast cell degranulation, fibroblast activation, and immunoglobulin deposits. This indolent and chronic "microinflammation" is not immediately destructive to the follicle as in lupus, but rather causes a dysregulation of normal physiologic dynamics of the hair cycle.[11,12,13,14,15,16] Ironically, this evolution in our understanding of the pathogenesis of AGA is very reminiscent of the change in our understanding of acne pathogenesis where the microinflammation is the source of all types of acne lesions including "non-inflammatory" ones.

Drug development has targeted specific pathways in the complex biology of hair growth with some success. However, the degree of benefit is variable from patient-to-patient, and long-term improvement requires long-term therapy with possible adverse events. Newer medical approaches to promoting healthy hair follicles and encouraging hair regrowth are embracing a multi-targeted approach that addresses the variety of complex factors that interact to influence the hair follicle. Treatments such as low-level light therapy, platelet-rich plasma, and nutraceuticals are used to target multiple parameters, including inflammation, and emerging as effective standalone or adjunct therapies to current pharmacologic options.[17,18,19]

Nutraceuticals contain potent botanicals with antioxidant and anti-inflammatory benefits to counter the effects of intrinsically and extrinsically mediated inflammation and ROS formation. This group also presents the only available option for addressing psycho-emotional stress and its impact on hair follicles. Select phytoactives with stress-adaptogenic properties have been shown to effect elevated cortisol levels and stabilize metabolic processes that confer greater resilience to stress.[20] As discussed ahead, these multi-targeting interventions can provide benefits at multiple steps in the complex microbiology of hair growth and can help to restore balance to the sensitive microenvironment of the hair follicle. Botanicals have an advantage to

be able to target multiple receptors and pathways at once, and also provide the opportunity to target some parameters of hair loss that are not currently addressed with prescription products as well as over the counter simple vitamins and minerals. However, due to lack of oversight and lack of standardization and clinical testing of botanicals, it is difficult to have a scientifically based nutraceutical. It is also unclear if any of the phytoactives in a particular supplement have preserved bioactivity post extraction with solvents, have significant absorption in the body, and are pure and free from additives and toxins. This is where Nutrafol® comes into the picture. Nutrafol® is a nutraceutical supplement with bio-optimized botanical ingredients that have clinical data on absorption and efficacy and is standardized to contain consistent fractions of phytoactive components.

I hope you will find our new perspective on pathogenesis of hair loss and our fresh look at the world of scientifically based nutraceuticals interesting and exciting.

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REFERENCES

1. Peters EM, Liotiri S, Bodo E, Hagen E, Biro T, Arck PC, et al. Probing the effects of stress mediators on the human hair follicle: substance P holds central position. *Am J Pathol.* 2007;171(6):1872-86.
2. Ito N, Ito T, Kromminga A, Bettermann A, Takigawa M, Kees F, et al. Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesize cortisol. *FASEB J.* 2005;19(10):1332-4.
3. Ito T. Hair follicle is a target of stress hormone and autoimmune reactions. *J Dermatol Sci.* 2010;60(2):67-73.
4. Bahta AW, Farjo N, Farjo B, Philpott MP. Premature senescence of balding dermal papilla cells in vitro is associated with p16(INK4a) expression. *J Invest Dermatol.* 2008;128(5):1088-94.
5. Trueb RM. Association between smoking and hair loss: another opportunity for health education against smoking? *Dermatology.* 2003;206(3):189-91.
6. Trueb RM. Oxidative stress in ageing of hair. *Int J Trichology.* 2009;1(1):6-14.
7. Breitkopf T, Leung G, Yu M, Wang E, McElwee KJ. The basic science of hair biology: what are the causal mechanisms for the disordered hair follicle? *Dermatol Clin.* 2013;31(1):1-19.
8. Trueb RM. Molecular mechanisms of androgenetic alopecia. *Exp Gerontol.* 2002;37(8-9):981-90.
9. Mahe YF, Michelet JF, Billoni N, Jarrousse F, Buan B, Commo S, et al. Androgenetic alopecia and microinflammation. *Int J Dermatol.* 2000;39(8):576-84.
10. Gatherwright J, Liu MT, Amirlak B, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to male alopecia: a study of identical twins. *Plast Reconstr Surg.* 2013;131(5):794e-801e.
11. El-Domyati M, Attia S, Saleh F, Abdel-Wahab H. Androgenetic alopecia in males: a histopathological and ultrastructural study. *J Cosmet Dermatol.* 2009;8(2):83-91.
12. Sueki H, Stoudemayer T, Kligman AM, Murphy GF. Quantitative and ultrastructural analysis of inflammatory infiltrates in male pattern alopecia. *Acta Derm Venereol.* 1999;79(5):347-50.
13. Deloche C, de Lacharriere O, Misciali C, Piraccini BM, Vincenzi C, Bastien P, et al. Histological features of peripilar signs associated with androgenetic alopecia. *Arch Dermatol Res.* 2004;295(10):422-8.
14. Jaworsky C, Kligman AM, Murphy GF. Characterization of inflammatory infiltrates in male pattern alopecia: implications for pathogenesis. *Br J Dermatol.* 1992;127(3):239-46.
15. Magro CM, Rossi A, Poe J, Manhas-Bhutani S, Sadick N. The role of inflammation and immunity in the pathogenesis of androgenetic alopecia. *J Drugs Dermatol.* 2011;10(12):1404-11.
16. Banka N, Bunagan MJ, Shapiro J. Pattern hair loss in men: diagnosis and medical treatment. *Dermatol Clin.* 2013;31(1):129-40.
17. Ablon G. A 6-month, randomized, double-blind, placebo-controlled study evaluating the ability of a marine complex supplement to promote hair growth in men with thinning hair. *J Cosmet Dermatol.* 2016;15(4):358-366.
18. Afifi L, Maranda EL, Zarei M, et al. Low-level laser therapy as a treatment for androgenetic alopecia. *Lasers Surg Med.* 2017;49(1):27-39.
19. Ferneini EM, Beauvais D, Castiglione C, Ferneini MV. Platelet-rich plasma in androgenic alopecia: indications, technique, and potential benefits. *J Oral Maxillofac Surg.* 2016.
20. Auddy B, et al. A standardized Withania somnifera extract significantly reduces stress-related parameters in chronically stressed humans: a double-blind, randomized, placebo-controlled study. *J Am Nutraceutical Assoc.* 2008;11(1):50-56.

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ORIGINAL ARTICLES Journal of Drugs in Dermatology

New Insight Into the Pathophysiology of Hair Loss Trigger a Paradigm Shift in the Treatment Approach

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ABSTRACT

Hair loss affects millions of men and women of all ages and ethnicities, impacting appearance, social interactions, and psycho-emotional well-being. Although a number of options are available, they are limited, carry a potential risk of side effects, and none have proven to be comprehensive for treatment of hair loss. Across the spectrum of hair loss disorders, there has long been a segmentation into distinct mechanisms, driving the main trend in current therapeutics to focus on targeting single molecules or pathways. However, research points to similar dysregulation of intrinsic signaling pathways within follicle physiology that span the hair loss disorder spectrum – with a common inflammatory component identified in most hair loss pathogenesis, including that of androgenetic alopecia (AGA).

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INTRODUCTION

Androgens, genetic susceptibility, chronic inflammation, oxidative stress, internal and external environmental triggers such as ultraviolet light, pollutants, aging, poor nutrition, as well as mediators of psycho-emotional stress (eg, cortisol and corticotropin releasing hormone) all contribute to dysregulation of complex follicle biology. Disruption of immune pathways affecting the follicle occurs through increased expression of pro-apoptotic and pro-inflammatory cytokines, perifollicular micro-inflammation, and release of reactive oxygen species (ROS). As we accept the multi-factorial nature driving hair loss, we can adopt new strategies to combat it, by aiming not at one, but at multiple targets. The rationale for this paradigm shift in hair loss therapy is the scope of this article. Herein is an update on our current understanding of hair physiology and the factors that have been scientifically demonstrated to influence hair follicle homeostasis and contribute to hair loss pathology.

Hair loss is chronic and progressive without treatment, affecting at least 50% of women by age 50 and 40% of men by age 35 (progressing to up to 70% in later life).[1-3] Hair is an important part of our appearance and social communication. It is therefore no surprise that its loss can cause significant psychological trauma in patients, which is further precipitated by the limited available treatment options that produce only variable results with chance for side effects.[2,4] Currently the only two FDA-approved drugs for hair loss are finasteride and minoxidil in men and only minoxidil in women.[5,6] The reason for lack of sustained, comprehensive, efficacious, and side effect-free therapies to date, may be the underappreciation of the impact and interplay of the multiple factors that influence the immunology and signaling pathways that regulate hair follicle biology.

As dermatologists we've traditionally segmented hair loss according to distinct causes and morphology, inflammatory vs. non-inflammatory, genetic vs. acquired, scarring vs. non-scarring, androgen-mediated vs. not.[7,8] This view has led to the design and development of drugs that target only single mechanisms, as exemplified by finasteride that inhibits production of dihydrotestosterone (DHT). However, recent research suggests that hair loss is multi-factorial and there may be more similarities than differences across the hair loss disorder spectrum. There is mounting evidence that just like most multigenic, chronic systemic and cutaneous disorders, hair loss is the result of an accumulation of multiple factors – genetic and environmental – that lead to the final molecular pathophysiology resulting in dysregulation of signaling pathways and inappropriate immune and inflammatory responses.[5,7-10] Chronic inflammation at the level of the follicle appears to be a common thread in all types of hair loss – a view supported by the wealth of research showing that even in traditionally 'non-inflammatory alopecias' like

androgenetic alopecia (AGA) there is a prominent micro-inflammatory and fibrotic component.[9,11] The observation that there are a plethora of mechanisms beyond androgens that contribute to hair loss lead many researchers to explore the role of inflammation and fibrosis in miniaturization of follicles,[12,13] and to identify their part in the pathogenesis of, and impediment to successful treatment of hair loss.[5]

Follicle immunology has thus become a topic of much hair research today as it is increasingly apparent that multiple immune driven pathways are involved in normal physiology of the follicle, as well as in the pathophysiology of hair loss when disrupted. Within the intrinsic follicular environment, multiple cytokines, growth and transcription factors signal the follicle to go into anagen vs. catagen phase and play a role in regeneration and renewal. In the event of micro-inflammation, overproduced cytokines like IL-1 and TNF-a are known to induce premature catagen, liberate ROS, cause apoptosis, and further propagate inflammation.[5,9] Likewise, factors like TGF-b are prominently overproduced by the dermal papilla cells in the presence of androgens and signal growth arrest, as well as play a role in perifollicular fibrosis and miniaturization.[14] These alterations in cytokine and protein expression – although not immediately destructive, over time chronically dysregulate physiological cycling dynamics and follicle stem cell homeostasis.[3,5,9,15-17] To this end, any therapy designed to comprehensively treat hair loss must address not only triggering factors but also their downstream signaling cascades, as well as mitigate inflammation.

Factors such as ultraviolet light, pollutants, toxins, stress, aging, smoking, antigenic exposure to bacteria, and fungi also generate ROS and promote a state of inflammation and oxidative stress in the follicle environment – contributing to hair loss.[18,19] Recent research has additionally elucidated the molecular mechanisms underlying the role of psycho-emotional stress in causing and exacerbating hair loss. Sustained and chronic stress can lead to perifollicular inflammation and disruption of follicle physiology via endocrine and neuroimmune mediators like corticotropin releasing hormone (CRH), cortisol, and substance P (SP), all of which have receptors on the follicle.[20,21,22]

As scientific research reveals more about hair follicle biology, we are compelled to look at the common thread within all hair disorders – the complex dysregulation of immune, inflammatory, and signaling cascades that regulate follicle homeostasis. Hence, any therapeutic that targets singular triggers such as androgens, without considering the pleiotropic downstream effects as well as the interplay of various signaling molecules, is destined to be incomplete. Further, the pathogenesis of hair loss is multi-factorial and requires a multimodal solution that can additionally address factors like stress, aging, environment and inflammation. In consequence, an updated look on hair loss therapeutics emerges, one that does not focus on singular targets (monotargeting), but comprehensively addresses the multiple factors that affect the follicle, the downstream deregulated follicle immunology and signaling, as well as inflammation. A thorough look at hair physiology and the triggers that deregulate it follows below, supporting the need for a paradigm shift in hair loss treatment towards multi-targeting therapeutic strategies.

The Regulation and Dysregulation of Hair Follicle Physiology – Consequences of Inflammation and Oxidative Stress

All phases of the hair cycle are subject to intrinsic controls that induce either anagen (growth) or catagen (regression and apoptosis), followed by telogen (rest), ensuring that under normal conditions shedding is followed by new growth. As hair loss is ultimately the result of premature entry into the catagen phase, identifying which signals control this is vital for considering therapeutics.[23] Growth in anagen is initiated by the dermal papilla cells (DPCs) which determine follicle and hair fiber characteristics, secrete mediators that regulate stem cells and influence growth of other follicular compartments.[24] Although the intricate machinery of the follicle hasn't been fully elucidated, a key signaling pathway regulating hair morphogenesis in anagen was identified to be the WNT pathway that mediates expression of a plethora of anagen-stimulating factors like IGF-1, bFGF, VEGF.[25-28] Conversely, catagen is believed to occur as a result of both decreases in expression of anagen-maintaining factors, as well as increase in expression of pro-apoptotic cytokines like TGF-b, IL-1, TNF-a.[29] Other controls intrinsically built into the follicle include its stem cell reservoirs and the hair follicle immune privilege (IP). The follicle being one of few sites in the body with IP, stresses the evolutionary importance of having it equipped with mechanisms for preventing the induction of both innate and adaptive immune responses. [30] The intrinsic mechanisms of the follicle are further subject to and integrated with signals from the macro-environment (eg, hormones, neurotransmitters) through endocrine, paracrine, and autocrine routes. As an example, androgens exert their effects via the DPCs, altering local immune balance by inducing DPC over-expression of catagen-promoting factors like TGF-b and other paracrine mediators that inhibit growth.[14,31,32] Aside from androgens, hair follicles express receptors for estrogens, cortisol, retinoids, insulin, thyroid hormones, vitamin D, and many other known and unknown factors – the full influence of which is still being investigated, but points to the fact that these affect intrinsic signaling pathways and that a balance of all is what ultimately determines hair growth.[14,31,32] Further, both follicles and other cells in the vicinity (eg, adipocytes, keratinocytes, fibroblasts, immune cells) also respond to systemic and environmental stimuli, generating mediators that shift local signaling, release ROS, and alter cycle control and growth.[5,8,33] In hair loss, whether it is sudden (anagen or telogen effluvium) where alteration in the cycles of numerous follicles happens concurrently, creating sudden diffuse shedding, or asynchronous and

gradual as with male pattern hair loss (MPHL)/female pattern hair loss (FPHL) where the duration of anagen is progressively shortened, while dormancy is increased - the compromise of intrinsic cycle controls and dysregulation of local follicle immune balance is inevitable.[5,8]

The immune system and inflammation are the body's primary defenses against noxious stimuli, as well as key mechanisms in healing. However, whereas acute inflammation can stimulate healing and in the case of follicles even lead to anagen induction, non-specific and chronic inflammation is a prolonged dysregulated cascade that suspends the body's normal responses, causing progressive damage. The prevalence of an inflammatory component in hair loss is underscored by the fact that it's observed in both traditionally 'inflammatory' and 'non-inflammatory' alopecias. Numerous histochemical, ultrastructural, and immunohistochemical studies have demonstrated perifollicular micro-inflammation in MPHL and FPHL presenting as lymphocytic infiltrates, mast cell degranulation, fibroblast activation, and immunoglobulin (IGM) deposits.[3,6,11,13,15,16] The term "micro-inflammation" was coined to allude to the indolent sub-clinical process of dysregulated chronic inflammation rather than the classic inflammatory attack seen on pathology in alopecia areata (AA), lupus, etc.[9] The basis for this phenomenon and its role in the pathogenesis of hair loss has been the subject of much research. In the instance of chronic processes like MPHL and FPHL, the micro-inflammatory component is localized to the vicinity of the bulge stem cell niche. The inflammatory processes, the release of ROS, and inflammatory mediators (eg, TNF-a, IL-1, histamine) alter the follicle immune milieu – and although not immediately destructive to the follicle, can over time dysregulate normal cycling dynamics and stem cell renewal.[5,9,11] In fact, studies show that biopsies from areas of clinically uninvolved scalp with high density scores in subjects with early AGA already demonstrate the presence of inflammatory infiltrates and fibrosis, indicating that micro-inflammation is not a secondary phenomenon but an active participant in pathogenesis.[3,8,15,16] A recent study also found a correlation between inflammatory infiltrates and apoptosis in miniaturized follicles, suggesting that inflammation can play a role in the pathogenesis of follicle miniaturization via activation of the extrinsic apoptotic pathway.[34] Further, sustained inflammatory processes also contribute to progressive perifollicular fibrosis.[9]

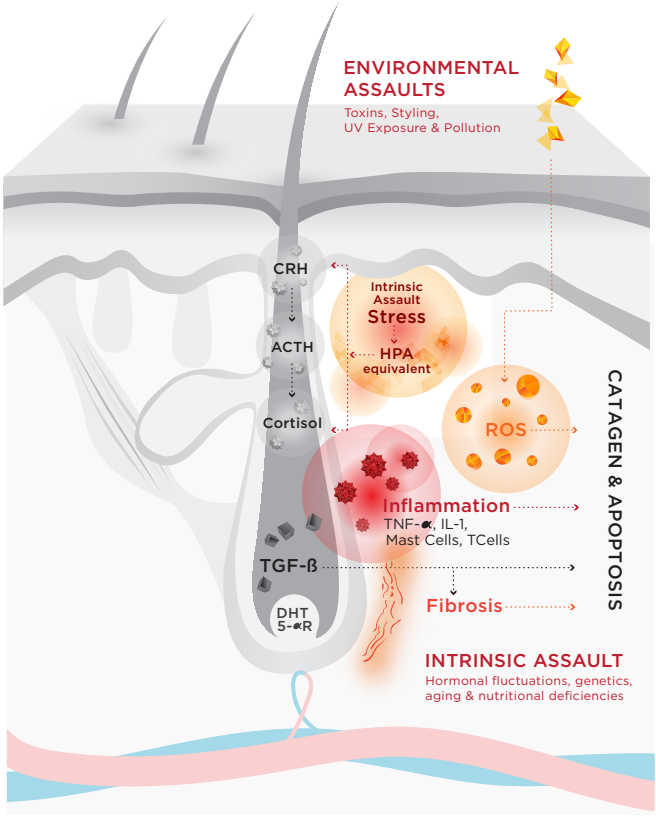
An important question is why the follicle becomes a target for an inflammatory reaction, whether it's micro-inflammation in AGA or an immune attack against self-antigens in AA. There are no definitive answers, but it is worth noting that inflammation is a multi-step process that may start from a primary event or a group of events, later perpetuated through a cyclic continuous cascade. In AGA for example, the localization of infiltrates to the upper follicle suggests the contribution of environmental factors in the inflammatory process. Colonization with normal microbial inhabitants or actual microbial toxins have been implicated.[8,9,11] Additionally keratinocytes have been shown to respond to irritants like UV irradiation, pollutants, and chemical or mechanical stresses by producing inflammatory cytokines and ROS.[5,9] Damage from free radicals triggers the release of inflammatory mediators, which thereby generate more ROS in a cyclic cascade. Oxidative stress overrides innate antioxidant defense mechanisms in aging cells and leads to apoptosis. In the case of the scalp, there is evidence it plays a pivotal role in hair greying and hair loss, where affected hair follicles were shown to be particularly vulnerable to ROS from environmental stressors.[23,35,36] Further, androgen signaling, TGF-b1, and mediators of stress have all been shown to be mediated via generation of ROS in the follicle – leading to growth arrest.[37,38] Aging hair exhibits up-regulation of oxidative stress and inflammatory response genes, predisposing follicles further.[35,36] And the compromise of regulatory mechanisms by psycho-emotional stress can also make follicles more susceptible to inflammatory attack, as in the case of AA.[8,20,22]

The presence and role of inflammation and oxidative stress cannot be ignored in the pathophysiology of hair loss and in the development of therapeutics. Adding anti-inflammatory therapies to treatment protocols of both AGA and trichotillomania with micro-inflammation lead to improved treatment outcomes.[11,39] Similarly, administration of anti-oxidants reversed the effects of oxidative stress on hair follicles in vitro and resulted in hair growth clinically.[37,38,40] This data supports the case for multi-targeted therapeutics for hair loss that can address the inflammatory and oxidative stress cascade, as well as the factors that precipitate it.

Consequences of Androgen Hormones

The fact that androgens influence hair growth has been known for ages. Androgen metabolism as well as androgen receptor (AR) levels and sensitivity are enhanced in balding scalp follicles in a spatial pattern in individuals with MPHL; and to a much lesser degree in FPHL, where the contribution of androgens is unclear, and stress, environment, and other hormones likely play a greater role.[34,41] Although the impact of androgens in the pathophysiology of hair disorders is the most elucidated of all hair loss triggers, ongoing research continuously reveals new molecular mechanisms behind androgen action. It is accepted now that the main target of androgens in hair follicles is the dermal papilla (DP), through which they induce secretion of autocrine and paracrine factors, dysregulating intrinsic signaling cascades that mediate hair growth.[17] Several factors induced from DP by androgens have been identified, with many more still to be discovered. It has been shown that androgens stimulate the DPCs to overproduce TGF-b, which is normally secreted to signal catagen and regression; and accordingly studies confirmed that androgen-induced TGF-b leads to catagen and suppression of follicular keratinocyte growth.[5,6,8,14,31] New research has

FIGURE 1. Multifactorial pathophysiology of hair loss.



identified that androgens also upregulate DPC production of WNT antagonist DKK-1, thus impairing hair follicle stem cell (HFSC) differentiation via dysregulation of WNT signaling, a pathway crucial for anagen entry.[17] Furthermore, once triggered, some other factors can maintain hair loss pathology without the presence of androgens, as seen in men castrated after puberty.[5,42] It is likely that the contribution of these downstream effectors to the dysregulation of follicle immune balance triggers a continuous cascade of immune and inflammatory processes that can progress even after androgens are removed. In fact, androgen-induced TGF-b was shown to induce oxidative stress in DPCs, as well as perifollicular fibrosis and inflammation via surrounding fibroblasts, thus playing a role in the chronic process of miniaturization.[38,43] Currently, pharmaceutical formulations only target one aspect of this signaling cascade – androgens. New insight into the mechanism however supports the use of multi-targeted therapeutics that can also target androgen receptors, gene expression, TGF-b, other downstream pro-apoptotic molecules, inflammatory cytokines, and oxidative stress.

Environmental vs. Genetic Triggers

Genetics play a role in all manifestations of hair loss and the genetic make-up of an individual can predispose them to any hair disorder (AGA, TE, AA).[8] AA clusters in families, and genetics also determine who will exhibit TE as a result of stress or another insult.[8] Although the genetics are far from being fully understood, it is now well accepted that, like most multifactorial chronic disorders with a variety of dysregulated signaling pathways, the mode of inheritance in hair loss is polygenic – dependent on multiple genes and interactions with the environment. In the case of FPHL and MPHL, although the androgen receptor was considered a main candidate gene in hair loss susceptibility, recent studies revealed several additional gene loci involving cell proliferation, perturbed neurological pathways, altered immune response, and WNT signaling – supporting androgen-independent mechanisms of predisposition, especially in FPHL.[5,44-46] The hair follicle is a conduit for intensive interactions with the internal and external environment. Although the effects of extrinsic and intrinsic factors are readily recognized in skin photoaging, their influence in hair loss is underappreciated.[47]

Large studies of identical twins with MPHL and FPHL showed that multiple non-genetic exogenous factors including smoking, absence of hat use, chronic stress, excessive alcohol consumption, and extreme exercise contributed significantly to the development and severity of hair loss.[10,48] Studies have shown that exposure to both extrinsic triggers (UV, pollutants, stress, tobacco, bacterial toxins, and antigens), as well as intrinsic factors (aging, poor nutrition) initiate perifollicular inflammatory signaling cascades that enhance pro-inflammatory gene expression and liberate ROS.[5,18,19,49] For example, exposure to UVR has been shown to trigger release of ROS and pro-inflammatory cytokines (eg, IL-1) in follicles and surrounding keratinocytes leading to apoptosis, cycle arrest, and injury of the putative site of follicular stem cells near the infundibulum.[5,9,49] It has been suggested that photoactivation of porphyrins from Propionibacterium spp. in the pilosebaceous duct can also contribute to oxidative tissue injury and follicular micro-inflammation.[9,50] Moreover, preclinical studies have illustrated that antioxidants provide photoprotection against oxidative damage.[1,35,47,51] While genetic predisposition is perhaps largely un-modifiable, genetic research has shown that epigenetic modification through environmental and endogenous factors can regulate gene expression, opening an opportunity to therapeutically intervene to rebalance the environment susceptible to hair loss by targeting inflammation, stress, and oxidative damage.[6]

Chronic Psycho-Emotional Stress (Cortisol and Other Stress Mediators)

Although clinical observations have provided anecdotal evidence into the brain-skin and brain-follicle axes, the molecular mechanisms underlying these connections have only recently been elucidated. Given the surrounding dense perifollicular meshwork of sensory nerve endings that are closely associated with mast cells and exhibit plasticity during chronic

stress, the follicles are a target of neuroimmunomodulatory and neuroinflammatory mediators like SP and nerve growth factor (NGF).[20,52-54] Studies have shown that psycho-emotional stress triggers systemic and local release of NGF (a catagen inducer) and SP from perifollicular nerve fibers, which leads to activation and degranulation of local mast cells that release a myriad of pro-inflammatory mediators like histamine and TNF-a – inducing neurogenic inflammation, release of ROS, early catagen, and hair growth arrest.[8,20,37,53-55] Moreover, SP was also found to up-regulate follicular expression of major histocompatibility complexes (MHC) that are normally down-regulated by hair follicles to maintain an immune privilege. Stress-mediated IP collapse renders the follicle open to activating inflammatory cascades and subsequent hair loss, a biologic imbalance that is implicated as the driving force in AA and scarring alopecias.[8,20,22]

As part of the neuroendocrine stress response, chronically elevated stress levels also lead to the production of excess systemic stress hormones, like cortisol, which are known to cause catagen, inhibit hair growth, and directly correlate with the development and exacerbation of hair loss disorders.[56,57] Furthermore, research has identified that the hair follicle is also uniquely equipped to produce its own stress hormones (ACTH, CRH, and cortisol) through an equivalent of the hypothalamic-pituitary-adrenal (HPA) axis, with established regulatory feedback loops.[21,22] At times of excess stress, systemic CRH binds to receptors on the follicle and stimulates the internal follicle hormone axis to produce ACTH, cortisol, and CRH locally - leading to further mast cell degranulation, inflammation, and apoptosis.[21,22]

Lending further evidence to the role of stress in dysregulation of follicle immune balance and perifollicular inflammation, a 2017 study of female medical students showed that prolonged life-stress exposure hampered hair growth, accompanied by significant fluctuations in TH1/TH2 cytokine balance compared to control group.[58] On a systemic level, chronically elevated cortisol levels (chronic stress) compromise the production and equilibrium of other hormones like TSH and thyroid hormones that are essential for proper hair follicle stem cell function and activation.[59] The sustained systemic endocrine disruption from elevated cortisol levels could provide further insight into poorly understood and complex processes like FPHL, and why these can be often precipitated by conditions that induce telogen effluvium. Stress is ubiquitous and the mechanisms through which the follicle is affected by it in one hair disorder apply to all hair disorders. Given the evidence above, managing and reducing stress levels, cortisol, SP, and the downstream mediators (inflammation, oxidative stress, destabilized mast cells, dysregulated immune signaling) should be a part of any hair loss treatment and prevention protocol. Since there are no pharmaceuticals that target stress, it would make sense to employ multi-targeting therapeutics with additional stress-adaptogenic properties.

CONCLUSION

The pathophysiology of hair loss is unequivocally multi-factorial and extremely complex, involving a plethora of factors and signaling pathways. Hormones, the brain-hair axis, and the environment-hair axis influence the hair follicle, chisel against its regulatory circuitry, and in the absence of strategies to counterbalance this attack, can ultimately override the hair follicle's internal controls. The result is a deleterious self-sustained inflammatory cascade as the new status quo (Figure 1). Restoring hair follicles to a state of homeostasis requires embracing a new outlook in terms of therapeutics. Current pharmaceutical interventions have limited success rate and possible side effects including sexual dysfunction and contact dermatitis. More importantly, these therapies focus on singular targets such as hair follicle testosterone metabolism, without considering the downstream effectors or the underlying pathophysiology of deregulated immune signaling and activated pro-inflammatory and pro-fibrotic cascades.

A paradigm shift in hair loss treatment is necessary, from monotargeting to multi-targeting therapeutic approaches that address not only androgens but also inflammation, oxidative stress, aging, elevated stress mediators like cortisol, their downstream signaling mediators, and also stimulate a nutrient-rich microenvironment in the hair follicle niche to promote repair and structural regeneration. Multi-targeted therapies such as platelet-rich plasma, low-level laser light and nutraceuticals are emerging and increasingly recognized for their efficacy as either standalone treatments or in combination with traditional hair loss protocols.[60-62] The common thread between these therapies is their multi-modal approach and focus on multiple signaling cascades, cytokines and growth factors that are altered in hair loss. In the next section we will review these novel therapy options, focusing on standardized nutraceuticals with their unique potential for synergistic, multi-targeted action of scientifically studied botanical phytochemicals.

DISCLOSURES

Dr. Sadick is the clinical investigator on the product. Dr. Kircik has received compensation from JDD for his editorial help. Dr. Callendar has no conflicts.

REFERENCES

1. Birch MP, Lashen H, Agarwal S, Messenger AG. Female pattern hair loss, sebum excretion and the end-organ response to androgens. *Br J Dermatol.* 2006;154(1):85-89.
2. Cash TF, Price VH, Savin RC. Psychological effects of androgenetic alopecia on women: comparisons with balding men and with female control subjects. *J Am Acad Dermatol.* 1993;29(4):568-575.
3. El-Domyati M, Attia S, Saleh F, Abdel-Wahab H. Androgenetic alopecia in males: a histopathological and ultrastructural study. *J Cosmet Dermatol.* 2009;8(2):83-91.
4. Hadshiew IM, Foitzik K, Arck PC, Paus R. Burden of hair loss: stress and the underestimated psychosocial impact of telogen effluvium and androgenetic alopecia. *J Invest Dermatol.* 2004;123(3):455-457.
5. Trueb RM. Molecular mechanisms of androgenetic alopecia. *Exp Gerontol.* 2002;37(8-9):981-990.

6. Banka N, Bunagan MJ, Shapiro J. Pattern hair loss in men: diagnosis and medical treatment. *Dermatol Clin.* 2013;31(1):129-140.
7. Qi J, Garza LA. An overview of alopecias. *Cold Spring Harb Perspect Med.* 2014;4(3).
8. Breitkopf T, Leung G, Yu M, Wang E, McElwee KJ. The basic science of hair biology: what are the causal mechanisms for the disordered hair follicle? *Dermatol Clin.* 2013;31(1):1-19.
9. Mahe YF, Michelet JF, Billoni N, et al. Androgenetic alopecia and microinflammation. *Int J Dermatol.* 2000;39(8):576-584.
10. Gatherwright J, Liu MT, Amirlak B, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to male alopecia: a study of identical twins. *Plast Reconstr Surg.* 2013;131(5):794e-801e.
11. Magro CM, Rossi A, Poe J, Manhas-Bhutani S, Sadick N. The role of inflammation and immunity in the pathogenesis of androgenetic alopecia. *J Drugs Dermatol.* 2011;10(12):1404-1411.
12. Whiting DA. Diagnostic and predictive value of horizontal sections of scalp biopsy specimens in male pattern androgenetic alopecia. *J Am Acad Dermatol.* 1993;28(5 Pt 1):755-763.
13. Jaworsky C, Kligman AM, Murphy GF. Characterization of inflammatory infiltrates in male pattern alopecia: implications for pathogenesis. *Br J Dermatol.* 1992;127(3):239-246.
14. Inui S, Fukuzato Y, Nakajima T, Yoshikawa K, Itami S. Identification of androgen-inducible TGF-beta1 derived from dermal papilla cells as a key mediator in androgenetic alopecia. *J Investig Dermatol Symp Proc.* 2003;8(1):69-71.
15. Sueki H, Stoudemayer T, Kligman AM, Murphy GF. Quantitative and ultrastructural analysis of inflammatory infiltrates in male pattern alopecia. *Acta Derm Venereol.* 1999;79(5):347-350.
16. Deloche C, de Lacharriere O, Misciali C, et al. Histological features of peripilar signs associated with androgenetic alopecia. *Arch Dermatol Res.* 2004;295(10):422-428.
17. Leiros GJ, Ceruti JM, Castellanos ML, Kusinsky AG, Balana ME. Androgens modify Wnt agonists/antagonists expression balance in dermal papilla cells preventing hair follicle stem cell differentiation in androgenetic alopecia. *Mol Cell Endocrinol.* 2017;439:26-34.
18. Kaya Erdogan H, Bulur I, Kocaturk E, Yildiz B, Saracoglu ZN, Alatas O. The role of oxidative stress in early-onset androgenetic alopecia. *J Cosmet Dermatol.* 2016.
19. Prie BE, Iosif L, Tivig I, Stoian I, Giurcaneanu C. Oxidative stress in androgenetic alopecia. *J Med Life.* 2016;9(1):79-83.
20. Peters EM, Liotiri S, Bodo E, et al. Probing the effects of stress mediators on the human hair follicle: substance P holds central position. *Am J Pathol.* 2007;171(6):1872-1886.
21. Ito N, Ito T, Kromminga A, et al. Human hair follicles display a functional equivalent of the hypothalamic-pituitary-adrenal axis and synthesize cortisol. *FASEB J.* 2005;19(10):1332-1334.
22. Ito T. Hair follicle is a target of stress hormone and autoimmune reactions. *J Dermatol Sci.* 2010;60(2):67-73.
23. Naito A, Midorikawa T, Yoshino T, Ohdera M. Lipid peroxides induce early onset of catagen phase in murine hair cycles. *Int J Mol Med.* 2008;22(6):725-729.
24. Zhang P, Kling RE, Ravuri SK, et al. A review of adipocyte lineage cells and dermal papilla cells in hair follicle regeneration. *J Tissue Eng.* 2014;5:2041731414556850.
25. Enshell-Seijffers D, Lindon C, Kashiwagi M, Morgan BA. beta-catenin activity in the dermal papilla regulates morphogenesis and regeneration of hair. *Dev Cell.* 2010;18(4):633-642.
26. Lee J, Tumbar T. Hairy tale of signaling in hair follicle development and cycling. *Semin Cell Dev Biol.* 2012;23(8):906-916.
27. Sennett R, Rendl M. Mesenchymal-epithelial interactions during hair follicle morphogenesis and cycling. *Semin Cell Dev Biol.* 2012;23(8):917-927.
28. Yang K, Wang X, Zhang H, et al. The evolving roles of canonical WNT signaling in stem cells and tumorigenesis: implications in targeted cancer therapies. *Lab Invest.* 2016;96(2):116-136.
29. Strauss RE. New concepts in the physiology and growth of hair. *Pa Med J.* 1954;57(5):441-443.
30. Christoph T, Muller-Rover S, Audring H, et al. The human hair follicle immune system: cellular composition and immune privilege. *Br J Dermatol.* 2000;142(5):862-873.
31. Itami S, Inui S. Role of androgen in mesenchymal epithelial interactions in human hair follicle. *J Investig Dermatol Symp Proc.* 2005;10(3):209-211.
32. Messenger AG, Sinclair R. Follicular miniaturization in female pattern hair loss: clinicopathological correlations. *Br J Dermatol.* 2006;155(5):926-930.
33. de Berker D, Higgins CA, Jahoda C, Christiano AM. Biology of hair and nails. In: Bolognia JL, Jorizzo JL, Schaffer JV, eds. *Dermatology.* Vol 1. 3 ed: Elsevier Health Sciences UK; 2012:1075-1092.
34. Ramos PM, Brianezi G, Martins AC, da Silva MG, Marques ME, Miot HA. Apoptosis in follicles of individuals with female pattern hair loss is associated with perifollicular microinflammation. *Int J Cosmet Sci.* 2016;38(6):651-654.
35. Trueb RM. Oxidative stress in ageing of hair. *Int J Trichology.* 2009;1(1):6-14.
36. Trueb RM. Pharmacologic interventions in aging hair. *Clin Interv Aging.* 2006;1(2):121-129.
37. Liu N, Wang LH, Guo LL, et al. Chronic restraint stress inhibits hair growth via substance P mediated by reactive oxygen species in mice. *PLoS One.* 2013;8(4):e61574.
38. Shin H, Yoo HG, Inui S, et al. Induction of transforming growth factor-beta 1 by androgen is mediated by reactive oxygen species in hair follicle dermal papilla cells. *BMB Rep.* 2013;46(9):460-464.
39. Oon HH, Lee JS. Treatment of pseudofolliculitis in trichotillomania improves outcome. *Int J Trichology.* 2011;3(2):92-95.
40. Beoy LA, Woei WJ, Hay YK. Effects of tocotrienol supplementation on hair growth in human volunteers. *Trop Life Sci Res.* 2010;21(2):91-99.
41. Messenger AG. Hair through the female life cycle. *Br J Dermatol.* 2011;165 Suppl 3:2-6.
42. Randall VA. Hormonal regulation of hair follicles exhibits a biological paradox. *Semin Cell Dev Biol.* 2007;18(2):274-285.
43. Yoo HG, Kim JS, Lee SR, et al. Perifollicular fibrosis: pathogenetic role in androgenetic alopecia. *Biol Pharm Bull.* 2006;29(6):1246-1250.
44. Dey-Rao R, Sinha AA. A genomic approach to susceptibility and pathogenesis leads to identifying potential novel therapeutic targets in androgenetic alopecia. *Genomics.* 2017;109(3-4):165-176.
45. Hagenaars SP, Hill WD, Harris SE, et al. Genetic prediction of male pattern baldness. *PLoS Genet.* 2017;13(2):e1006594.
46. Heilmann-Heimbach S, Herold C, Hochfeld LM, et al. Meta-analysis identifies novel risk loci and yields systematic insights into the biology of male-pattern baldness. *Nat Commun.* 2017;8:14694.
47. Trueb RM. Is androgenetic alopecia a photoaggravated dermatosis? *Dermatology.* 2003;207(4):343-348.
48. Gatherwright J, Liu MT, Gliniak C, Totonchi A, Guyuron B. The contribution of endogenous and exogenous factors to female alopecia: a study of identical twins. *Plast Reconstr Surg.* 2012;130(6):1219-1226.
49. Furness DN. Molecular basis of hair cell loss. *Cell Tissue Res.* 2015;361(1):387-399.
50. Trueb RM. The impact of oxidative stress on hair. *Int J Cosmet Sci.* 2015;37 Suppl 2:25-30.
51. Fernandez E, Martinez-Teipel B, Armengol R, Barba C, Coderch L. Efficacy of antioxidants in human hair. *J Photochem Photobiol B.* 2012;117:146-156.
52. Paus R, Theoharides TC, Arck PC. Neuroimmunoendocrine circuitry of the 'brain-skin connection'. *Trends Immunol.* 2006;27(1):32-39.
53. Baluk P. Neurogenic inflammation in skin and airways. *J Investig Dermatol Symp Proc.* 1997;2(1):76-81.
54. Peters EM, Arck PC, Paus R. Hair growth inhibition by psychoemotional stress: a mouse model for neural mechanisms in hair growth control. *Exp Dermatol.* 2006;15(1):1-13.
55. Arck PC, Handjiski B, Peters EM, et al. Stress inhibits hair growth in mice by induction of premature catagen development and deleterious perifollicular inflammatory events via neuropeptide substance P-dependent pathways. *Am J Pathol.* 2003;162(3):803-814.
56. Thom E. Stress and the hair growth cycle: Cortisol-induced hair growth disruption. *J Drugs Dermatol.* 2016;15(8):1001-1004.
57. Schmidt JB. Hormonal basis of male and female androgenic alopecia: clinical relevance. *Skin Pharmacol.* 1994;7(1-2):61-66.
58. Peters EMJ, Muller Y, Snaga W, et al. Hair and stress: A pilot study of hair and cytokine balance alteration in healthy young women under major exam stress. *PLoS One.* 2017;12(4):e0175904.
59. Contreras-Jurado C, Lorz C, Garcia-Serrano L, Paramio JM, Aranda A. Thyroid hormone signaling controls hair follicle stem cell function. *Mol Biol Cell.* 2015;26(7):1263-1272.
60. Ablon G. A 6-month, randomized, double-blind, placebo-controlled study evaluating the ability of a marine complex supplement to promote hair growth in men with thinning hair. *J Cosmet Dermatol.* 2016;15(4):358-366.
61. Afifi L, Maranda EL, Zarei M, et al. Low-level laser therapy as a treatment for androgenetic alopecia. *Lasers Surg Med.* 2017;49(1):27-39.
62. Ferneini EM, Beauvais D, Castiglione C, Ferneini MV. Platelet-rich plasma in androgenic alopecia: Indications, technique, and potential benefits. *J Oral Maxillofac Surg.* 2016.

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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.

J Drugs Dermatol. 2017;16(11 Suppl):s141-148.

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.

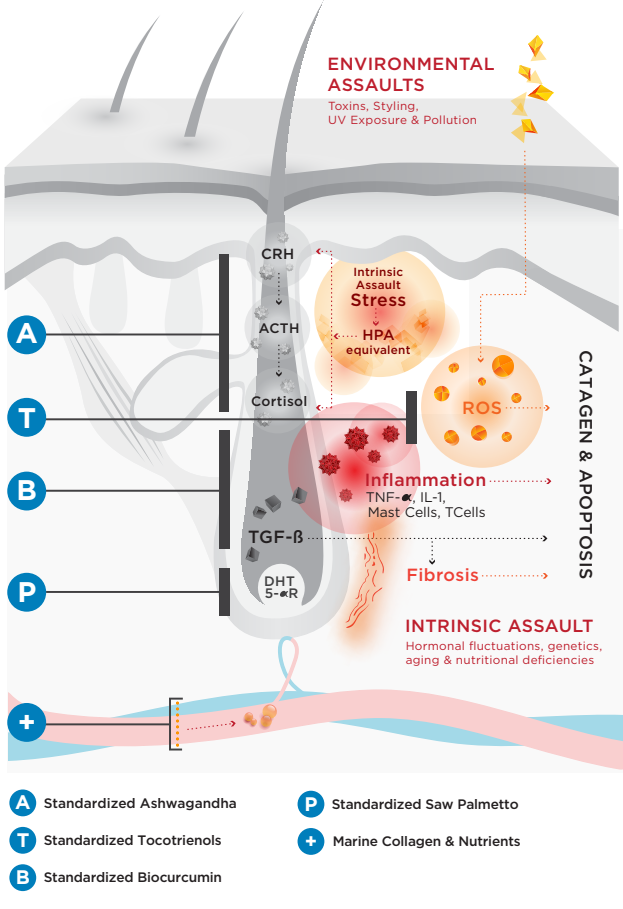


TABLE 1.

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.

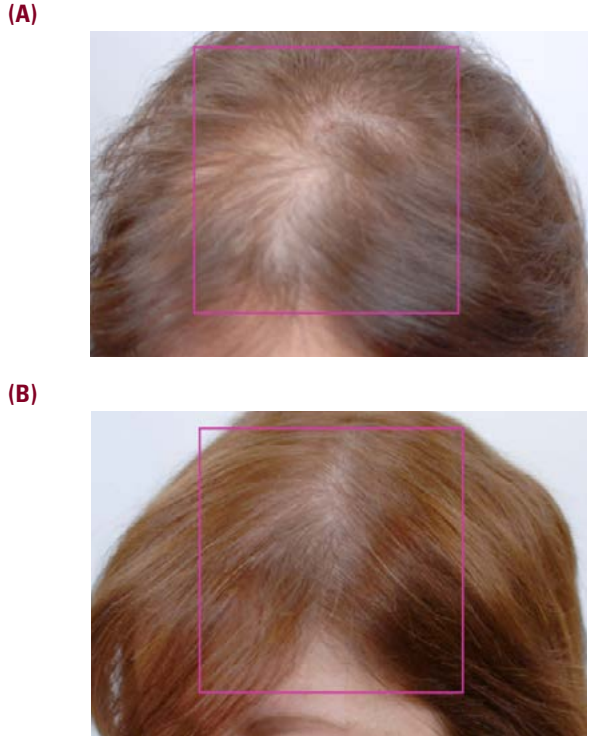
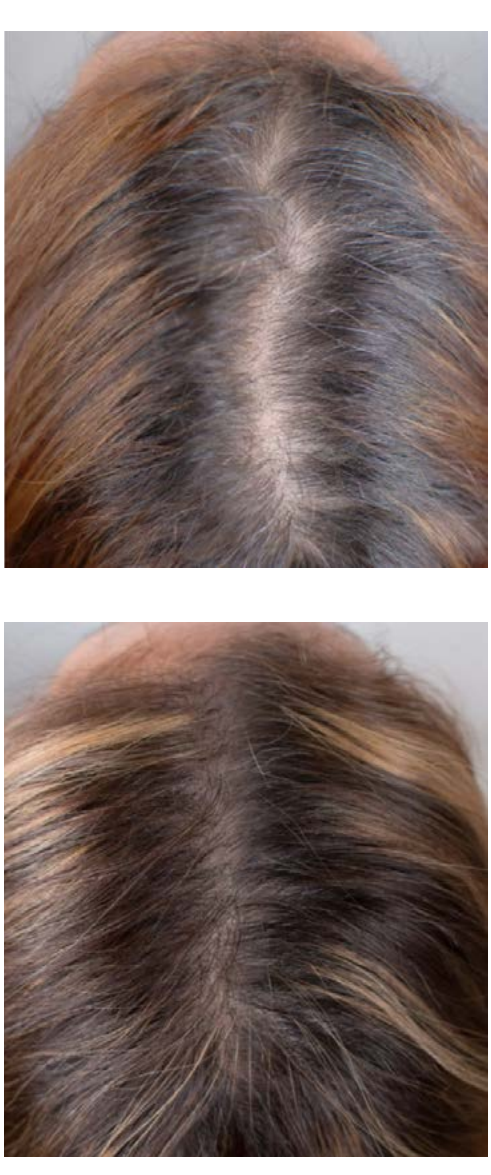


FIGURE 3. 45-year-old woman (A) before and (B) at four months of treatment.



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

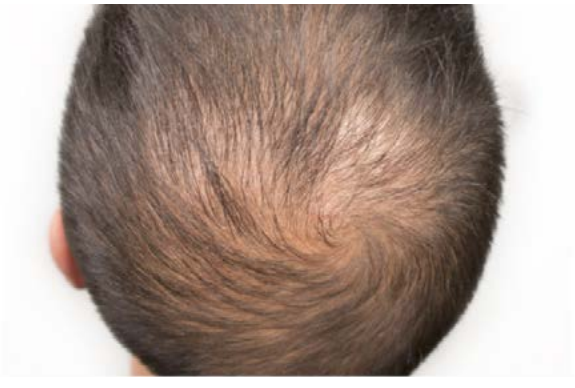
A 52-year-old woman before and after two years of Nutrafol® use (Figure 2). She had a history of chronic anemia, now resolved, and diverticulitis. She takes no medications. Her family history includes early hair loss in father, sister, and brother and she believes stress and childbearing triggered her 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.

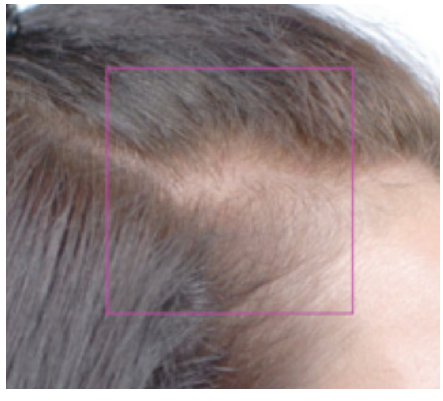
(A)



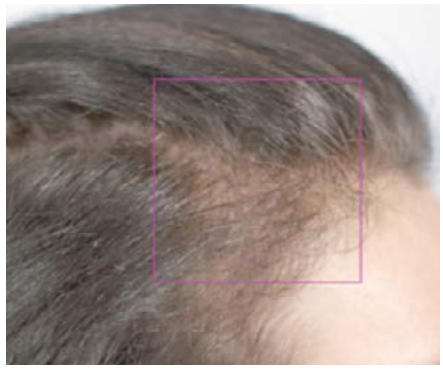
(B)

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.

REFERENCES

1. Anunciato TP, da Rocha Filho PA. Carotenoids and polyphenols in nutricosmetics, nutraceuticals, and cosmeceuticals. *J Cosmet Dermatol.* 2012;11(1):51-54.
2. Guo EL, Katta R. Diet and hair loss: effects of nutrient deficiency and supplement use. *Dermatol Pract Concept.* 2017;7(1):1-10.
3. Brown AC. An overview of herb and dietary supplement efficacy, safety and government regulations in the United States with suggested improvements. Part 1 of 5 series. *Food Chem Toxicol.* 2016.
4. Gan DC, Sinclair RD. Prevalence of male and female pattern hair loss in Maryborough. *J Investig Dermatol Symp Proc.* 2005;10(3):184-189.
5. Hunt N, McHale S. The psychological impact of alopecia. *BMJ.* 2005;331(7522):951-953.
6. Cash TF, Price VH, Savin RC. Psychological effects of androgenetic alopecia on women: comparisons with balding men and with female control subjects. *J Am Acad Dermatol.* 1993;29(4):568-575.
7. Hadshiew IM, Foitzik K, Arck PC, Paus R. Burden of hair loss: stress and the underestimated psychosocial impact of telogen effluvium and androgenetic alopecia. *J Invest Dermatol.* 2004;123(3):455-457.
8. Rogers NE AM. Medical treatments for male and female pattern hair loss. *J Am Acad Dermatol.* 2008;59(4):20.
9. Blume-Peytavi U, Hillmann K, Dietz E, Canfield D, Garcia Bartels N. A randomized, single-blind trial of 5% minoxidil foam once daily versus 2% minoxidil solution twice daily in the treatment of androgenetic alopecia in women. *J Am Acad Dermatol.* 2011;65(6):1126-1134 e1122.
10. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. *Br J Dermatol.* 2004;150(2):186-194.
11. Mella JM, Perret MC, Manzotti M, Catalano HN, Guyatt G. Efficacy and safety of finasteride therapy for androgenetic alopecia: a systematic review. *Arch Dermatol.* 2010;146(10):1141-1150.
12. Dawber RP, Rundegren J. Hypertrichosis in females applying minoxidil topical solution and in normal controls. *J Eur Acad Dermatol Venereol.* 2003;17(3):271-275.
13. Friedman ES, Friedman PM, Cohen DE, Washenik K. Allergic contact dermatitis to topical minoxidil solution: etiology and treatment. *J Am Acad Dermatol.* 2002;46(2):309-312.
14. Prahalada S, Tarantal AF, Harris GS, et al. Effects of finasteride, a type 2 5-alpha reductase inhibitor, on fetal development in the rhesus monkey (Macaca mulatta). *Teratology.* 1997;55(2):119-131.
15. Kiguradze T, Temps WH, Yarnold PR, et al. Persistent erectile dysfunction in men exposed to the 5alpha-reductase inhibitors, finasteride, or dutasteride. *PeerJ.* 2017;5:e3020.
16. Traish AM, Hassani J, Guay AT, Zitzmann M, Hansen ML. Adverse side effects of 5alpha-reductase inhibitors therapy: persistent diminished libido and erectile dysfunction and depression in a subset of patients. *J Sex Med.* 2011;8(3):872-884.
17. Gur S KP, Hellstron WJ. Effects of 5-alpha reductase inhibitors on erectile function, sexual desire, and ejaculation. *Expert Opin Drug Saf* 2014;12(1):10.
18. Beitkopf T LG, Yu M, et al. The basic science of hair biology. What are the causal mechanisms for the disordered hair follicle? *Derm Clinic.* 2013;31:1-19.
19. Magro CM, Rossi A, Poe J, Manhas-Bhutani S, Sadick N. The role of inflammation and immunity in the pathogenesis of androgenetic alopecia. *J Drugs Dermatol.* 2011;10(12):1404-1411.
20. Upton JH, Hannen RF, Bahta AW, Farjo N, Farjo B, Philpott MP. Oxidative stress-associated senescence in dermal papilla cells of men with androgenetic alopecia. *J Invest Dermatol.* 2015;135(5):1244-1252.
21. Ramos PM, Brianezi G, Martins AC, da Silva MG, Marques ME, Miot HA. Apoptosis in follicles of individuals with female pattern hair loss is associated with perifollicular microinflammation. *Int J Cosmet Sci.* 2016;38(6):651-654.
22. Trueb RM. The impact of oxidative stress on hair. *Int J Cosmet Sci.* 2015;37 Suppl 2:25-30.
23. Choudhry SZ, Bhatia N, Ceilley R, et al. Role of oral Polypodium leucotomos extract in dermatologic diseases: a review of the literature. *J Drugs Dermatol.* 2014;13(2):148-153.
24. Ni Z, Mu Y, Gulati O. Treatment of melasma with Pycnogenol. *Phytother Res.* 2002;16(6):567-571.
25. Middelkamp-Hup MA, Bos JD, Rius-Diaz F, Gonzalez S, Westerhof W. Treatment of vitiligo vulgaris with narrow-band UVB and oral Polypodium leucotomos extract: a randomized double-blind placebo-controlled study. *J Eur Acad Dermatol Venereol.* 2007;21(7):942-950.
26. Goel A KA, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. *Biochem Pharmacol.* 2008;75(4):787-809.
27. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. *AAPS J.* 2013;15(1):195-218.
28. Fadus MC LC, Bikhchandi, Lynch H. Curcumin; An age-old anti-inflammatory and anti-neoplastic agent. *J Trad Comp Med.* 2016.
29. Liu Z, Dou W, Zheng Y, et al. Curcumin upregulates Nrf2 nuclear translocation and protects rat hepatic stellate cells against oxidative stress. *Mol Med Rep.* 2016;13(2):1717-1724.
30. Nakamura K, Yasunaga Y, Segawa T, et al. Curcumin down-regulates AR gene expression and activation in prostate cancer cell lines. *Int J Oncol.* 2002;21(4):825-830.
31. Shishodia S. Molecular mechanisms of curcumin action: gene expression. *Biofactors.* 2013;39(1):37-55.
32. Jang S, Lee Y, Hwang SL, et al. Establishment of type II 5alpha-reductase over-expressing cell line as an inhibitor screening model. *J Steroid Biochem Mol Biol.* 2007;107(3-5):245-252.
33. Suphrom N, Pumthong G, Khorana N, Waranuch N, Limpeanchob N, Ingkaninan K. Anti-androgenic effect of sesquiterpenes isolated from the rhizomes of Curcuma aeruginosa Roxb. *Fitoterapia.* 2012;83(5):864-871.
34. Pumthong G, Asawanonda P, Varothai S, et al. Curcuma aeruginosa, a novel botanically derived 5alpha-reductase inhibitor in the treatment of male-pattern baldness: a multicenter, randomized, double-blind, placebo-controlled study. *J Dermatolog Treat.* 2012;23(5):385-392.
35. Huh S, Lee J, Jung E, et al. A cell-based system for screening hair growth-promoting agents. *Arch Dermatol Res.* 2009;301(5):381-385.
36. Arck PC, Slominski A, Theoharides TC, Peters EMJ, Paus R. Neuroimmunology of Stress: Skin Takes Center Stage. *J Invest Dermatol.* 2006;126(8):1697-1704.
37. Thom E. Stress and the Hair Growth Cycle: Cortisol-Induced Hair Growth Disruption. *J Drugs Dermatol.* 2016;15(8):1001-1004.
38. Finn DF, Walsh JJ. Twenty-first century mast cell stabilizers. *Br J Pharmacology.* 2013;170(1):23-37.
39. Nishikawa H, Tsutsumi J, Kitani S. Anti-inflammatory and anti-oxidative effect of curcumin in connective tissue type mast cell. *Journal of Functional Foods.* 2013;5(2):763-772.
40. Arora V, Kuhad A, Tiwari V, Chopra K. Curcumin ameliorates reserpine-induced pain-depression dyad: behavioural, biochemical, neurochemical and molecular evidences. *Psychoneuroendocrinology.* 2011;36(10):1570-1581.
41. Panahi Y, Sahebkar A, Amiri M, et al. Improvement of sulphur mustard-induced chronic pruritus, quality of life and antioxidant status by curcumin: results of a randomised, double-blind, placebo-controlled trial. *Br J Nutrition.* 2011;108(7):1272-1279.
42. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. *Mol Pharm.* 2007;4(6):807-818.
43. Pan MH, Huang TM, Lin JK. Biotransformation of curcumin through reduction and glucuronidation in mice. *Drug Metab Dispos.* 1999;27(4):486-494.
44. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Med.* 1998;64(4):353-356.
45. Antony B, Merina B, Iyer VS, Judy N, Lennertz K, Joyal S. A Pilot Cross-Over Study to Evaluate Human Oral Bioavailability of BCM-95CG (Biocurcumax), A Novel Bioenhanced Preparation of Curcumin. *Indian J Pharm Sci.* 2008;70(4):445-449.
46. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. *Phytother Res.* 2012;26(11):1719-1725.
47. Bhattacharya SK, Muruganandam AV. Adaptogenic activity of Withania somnifera: an experimental study using a rat model of chronic stress. *Pharmacol Biochem Behav.* 2003;75(3):547-555.
48. Singh G SP, Dudhe R, Singh S. Biological activities of Withania somnifera. *Ann Biol Res.* 2010:56-63.
49. Auddy B HJ, Mitra A, Abedon B, Ghosal S. A standardized Withania somnifera extract significantly reduces stress-related parameters in chronically stressed humans: a double-blind, randomized, placebo-controlled study. *J Am Nutraceut Assoc.* 2008;11(1):50-66.
50. Snehal S. Patel JKS. Systematic review of plant steroids as potential anti-inflammatory agents: Current status and future perspectives. *The Journal of Phytopharmacology.* 2015;4(2):121-125.
51. Bhattacharya SK GR, Kaur R, Ghosal S. Anti - stress activity of Sitoindosides VII and VIII. New Acylsterylglucosides from Withania somnifera. *Phytother Res* 1987;1:32-37.
52. Dar NJ, Hamid A, Ahmad M. Pharmacologic overview of Withania somnifera, the Indian Ginseng. *Cell Mol Life Sci.* 2015;72(23):4445-4460.
53. Ruchi Tiwari SC SM, Dhara K et al. Ashwagandha (Withania somnifera): role in safeguarding health, immunomodulatory effect, combating infections and therapuetic applications: A review. *Jour Biol Sci* 2014;14(2):77-94.
54. Pingali Usharani NF. Evaluation of a highly standardized Withania somnifera extract on endothelial dysfunction and biomarkers of oxidative stress in patients with type 2 diabetes mellitus: a randomized, double blind, placebo controlled study. *Int J Ayur Pharma Res.* 2014;2(3):22-32.

55. Suter A, Saller R, Riedi E, Heinrich M. Improving BPH symptoms and sexual dysfunctions with a saw palmetto preparation? Results from a pilot trial. *Phytother Res.* 2013;27(2):218-226.
56. Ooi SL, Pak SC. Serenoa repens for Lower Urinary Tract Symptoms/Benign Prostatic Hyperplasia: Current Evidence and its Clinical Implications in Naturopathic Medicine. *J Altern Complement Med.* 2017.
57. Prager N, Bickett K, French N, Marcovici G. A randomized, double-blind, placebo-controlled trial to determine the effectiveness of botanically derived inhibitors of 5-alpha-reductase in the treatment of androgenetic alopecia. *J Altern Complement Med.* 2002;8(2):143-152.
58. Rossi A EM, et al. . Comparative effectiveness of finasteride and serenoa repens in male androgenetic alopecia: a two year study. . *International Journal of Immunopathology and Pharmacology.* 2012;25(4).
59. Yang S, Chen C, Li Y, et al. Saw palmetto extract enhances erectile responses by inhibition of phosphodiesterase 5 activity and increase in inducible nitric oxide synthase messenger ribonucleic acid expression in rat and rabbit corpus cavernosum. *Urology.* 2013;81(6):1380 e1387-1313.
60. Habib FK, Ross M, K.H. Ho C, Lyons V, Chapman K. Serenoa repens (Permixon®) inhibits the 5α-reductase activity of human prostate cancer cell lines without interfering with PSA expression. *International Journal of Cancer.* 2005;114(2):190-194.
61. AM. P. Vitamin E. Tocopherols and Tocotrienols. Antioxidant status, diet, nutrition, and health. *CRC Press.*198-210.
62. Serbinova E, Kagan V, Han D, Packer L. Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol. *Free Radic Biol Med.* 1991;10(5):263-275.
63. Ahsan H, Ahad A, Iqbal J, Siddiqui WA. Pharmacological potential of tocotrienols: a review. *Nutr Metab (Lond).* 2014;11(1):52.
64. Naziroglu M, Kokcam I. Antioxidants and lipid peroxidation status in the blood of patients with alopecia. *Cell Biochem Funct.* 2000;18(3):169-173.
65. Beoy LA, Woei WJ, Hay YK. Effects of tocotrienol supplementation on hair growth in human volunteers. *Trop Life Sci Res.* 2010;21(2):91-99.
66. Wang Y, Park NY, Jang Y, Ma A, Jiang Q. Vitamin E gamma-Tocotrienol Inhibits Cytokine-Stimulated NF-kappaB Activation by Induction of Anti-Inflammatory A20 via Stress Adaptive Response Due to Modulation of Sphingolipids. *J Immunol.* 2015;195(1):126-133.
67. Kesarwani K, Gupta R, Mukerjee A. Bioavailability enhancers of herbal origin: an overview. *Asian Pac J Trop Biomed.* 2013;3(4):253-266.
68. McNamara FN RA, Gunthorpe MJ. Effects of piperine, the pungent component of black pepper, at the human vanilloid receptor (TRPV1). *Br J Pharmacol.* 2005;144(6):781-790.
69. (ed.) PSL. The Gastrointestinal System: Gastrointestinal, Nutritional, and Hepatobiliary Physiology. *Springer Science + Business Media Dordrecht.* 2014:35-62.
70. Atal N, Bedi KL. Bioenhancers: Revolutionary concept to market. *J Ayurveda Integr Med.* 2010;1(2):96-99.
71. Frantz C, Stewart KM, Weaver VM. The extracellular matrix at a glance. *J Cell Sci.* 2010;123(Pt 24):4195-4200.
72. Watanabe-Kamiyama M, Shimizu M, Kamiyama S, et al. Absorption and effectiveness of orally administered low molecular weight collagen hydrolysate in rats. *J Agric Food Chem.* 2010;58(2):835-841.
73. Matsuda N, Koyama Y, Hosaka Y, et al. Effects of ingestion of collagen peptide on collagen fibrils and glycosaminoglycans in the dermis. *J Nutr Sci Vitaminol (Tokyo).* 2006;52(3):211-215.
74. Zhuang Y HH, Zhao X et al. Effect of collagen and collagen hydrolysates from jellyfish (Rhopilema esculentum) on mice skin photoaging induced by UV irradiation. *J Food Sci.* 2009;74:H183-H188.
75. Tana M KY-I, Nomura Y. . Effect of collagen peptide ingestion of UVB-induced skin damage. *Biosci Biotechnol Biochem.* 2009;73:930-932.
76. G A. A double-blind, placebo-controlled study evaluating the efficacy of an oral supplement in women with self-perceived thinning hair. *J Clin Aesthet Dermatol.* 2012;5:28-34.
77. Lassus A EE. Treatment of hereditary androgenetic alopecia in young males. *International Med Res.* 1992;20:445-453.

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