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Hair Loss Treatment Shows Anti-inflammatory Activity *in vitro*

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Currently, the typical regimen for patients undergoing transplant surgery is either minoxidil and/or finasteride -- or possibly dutasteride. A word of caution with all current drug-based options is the potential for negative side effects. Alternatively, in the past decade a series of hair loss treatments have been developed containing natural compounds and phytochemicals. These generally offer an excellent safety profile, however, with rare exception, they remain largely unsupported by peer-reviewed data.

The development of safe and highly effective treatments for pattern hair loss thus remains a challenging goal. While the genetic basis of androgenetic alopecia (AGA) has not yet been completely determined, it is clearly a complex genetic disorder in which multiple genes, hormonal pathways and environmental factors contribute to phenotype. To date, DHT modulation via 5-AR blockade remains the main target for medical therapy shown to slow the progression of AGA.

Previously, in a small IRB-monitored trial, we tested the efficacy of the liposterolic extract of Serenoa repens (LSESr), aka saw palmetto extract, aka Permixon and its glycoside, β-sitosterol, in subjects with AGA and showed a highly positive response to treatment. The resulting publication in 2002 [1] established the effectiveness of naturally occurring 5-AR inhibitors against AGA for the first time. LSESr, sourced from the fruit of the saw palmetto tree contains a veritable stew of bioactive fatty acids and sterols, including stigmasterol, campesterol, and β-sitosterol.

Saw palmetto first came into widespread clinical use in Europe as a demonstrably safe and effective treatment for benign prostatic hyperplasia (BPH) [2]. Notably, in a direct comparison of LSESr against finasteride, it has been reported that LSESr exhibited a 3-fold greater inhibition of 5-AR in vitro assays [3]. No published BPH or AGA studies have thus far directly compared finasteride to LSESr, although this would, without doubt, constitute a rational analysis.

But clearly blockade of 5-AR treats only one aspect of AGA. Chronic inflammation is recognized at the molecular and cellular levels as the final common pathway of many systemic and degenerative diseases, including those affecting skin. It has also been observed that inflammation plays a role as a contributing factor to common pattern hair loss. Histologically, sustained follicular inflammation is a known finding in AGA.

To interrogate this hypothesis, we tested a proprietary formulation containing LSESr, L-carnitine and thioctic acid (TA) in a well-validated in vitro assay representative of HF keratinocytes, specifically, LPS-stimulated HaCaT cells. Our rationale was based on the understanding that L-carnitine, TA and LSESr operate through distinct, but potentially interrelated, biochemical and molecular mechanisms. For instance, accumulating evidence suggests that L-carnitine may play a significant role in prevention and treatment of numerous diseases as well as protection from accelerated aging that result from oxygen free-radical damage, inflammation and glycation (non-enzymatic glycosylation).

One line of research suggests that carnitine may possess the ability to promote hair growth in vitro by increasing energy supply to the rapidly proliferating and energy-consuming anagen hair matrix [4]. Likewise, TA is now recognized as a compound with many biological functions, such as the modulation of pathogenic inflammatory events, including those in the skin. Our hypothesis hinges on the enhanced efficacy of combining anti-inflammatory agents with 5-AR inhibitors.

We tested for changes in gene expression across a spectrum of well-characterized inflammatory markers and found that our test compound demonstrates statistically significant anti-inflammatory properties in vitro. For example, we noted that the composition effectively suppressed LPS-activated gene expression of chemokines CCL17, CXCL6 and Leucotriene (LT) B4. The over-expression of each of these markers has previously been observed in the setting of hair follicle inflammation and cellular apoptosis.

In a recently published monograph we showed that HaCaT cells treated with 100 ng LPS inflammatory agonist displayed an up-regulated fold change for (LT) B4 of 1.33 when measured against baseline [5]. In the same study, gene expression of (LT) B4 was down-regulated 2.64-fold in the cells treated with the test compound alone. LPS incubated cells showed upregulation of (LT) B4. However, challenge of these same cells with the test compound showed marked change in (LT) B4 expression demonstrating a 4.59-fold reduction in gene expression as measured against baseline. In sum, these results show that our compound convincingly blocked the LPS-stimulated up-regulation of the inflammatory marker (LT) B4.

Recognizing that inflammation contributes to a wide range of diseases, including those affecting the skin and hair, it is our view that the blockade of inflammation in susceptible hair follicles represents a new and potentially viable therapeutic avenue. The enhanced outcome potential for using anti-inflammatory compounds with 5-AR inhibitors is amenable for testing in the setting of transplant surgery. Since, in our opinion, the clinical success rate for treatment of AGA with androgen blockade alone is limited, there is enormous unmet medical need for patients who are refractory to current therapy.

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