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Case Report

Unique Herbal-Based Topical Is Comparable to Prescription Retinoid's Impact on Photoaging and Repair Biomarkers

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Abstract

A randomized controlled blinded pilot trial to evaluate the expression of key biomarkers of a topical cream comprising a unique blend of Herbal Extracts (HE) providing anti-inflammatory and stratum corneum repair compared to Tretinoin (Tr) 0.02% cream. Eight peri and post-menopausal women of skin types I-III with moderate to severe photodamage on forearms were evaluated. Two biomarkers for presence of photoaging revealed no statistically significant difference ($p < 0.05$) between HE and the prescription Tr product . These biomarkers include Fibrillin Ab and procollagen 2. Peroxisome Proliferator Activated Receptor (PPAR) gamma which is a biomarker for epidermal and stratum corneum repair was also tested. Compared to Tr, HE reached a trend toward statistical significance ($p = 0.075$) superiority in modulating PPAR gamma.

Introduction

It has long been known that chronic exposure to natural sunlight is the major driver of photoaging [1]. In the last 15 years, airborne pollution and tobacco smoke have also been proven to induce skin aging [2,3]. Of course, genetic variants are also significant contributors to skin aging. Sunscreens used daily significantly reduce photoaging in as little as four years [1]. Vitamin A and its derivatives are considered the gold standard to reverse and prevent photoaging to a significant degree but do not completely reverse the visible signs of it. This problem arises from the photosensitivity of vitamin A metabolic products and the compromised integrity and function of the stratum corneum barrier. The anomalies induce the commonly seen erythema, scaling, irritation and burning with topical application. The incidence is up to 40% [4,5]. Tretinoin (Tr) is the final metabolite of vitamin A used in human cells. The topical products incorporating this bioactive are all prescription. Its precursors of retinol, beta carotene and retinaldehyde do not require prescription thus are frequently incorporated into cosmeceuticals. Tr is the bioactive molecule used in the first FDA product be approved to treat wrinkles about two decades ago. The growing interest in herbal topical therapies has led to nearly a thousand studies being published since 2017 on reversing skin aging .

Increasing interest in herbal topical therapies has resulted in nearly a thousand studies published since 2017 for reversing skin aging [6]. The herbal extract product was designed to reverse photoaging by repairing and optimizing stratum corneum barrier function, mitigate cutaneous inflammatory reactions, prevent photosensitivity while upregulating all five epidermal strata structure and function. The purpose of this trial is to compare the effect upon molecular biomarkers indicating severity of photoaging and ability to repair the epidermis damaged from environmental insults. HE and Tr were compared in a 12-day occlusive patch followed by biopsy in a paired comparison clinical trial. HE was previously documented to have a negative Repeat Insult patch test indicating no sensitization nor irritation with this product.

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Higher concentrations of Tr were not used due to significantly increased risk of irritation with occlusion.

Methods and materials

Institutional Review Board approval was obtained for ethical considerations. The volunteer subjects all consented to this study and its publications. The IRB was conducted by Advarra: #Pro000068962.

Eight subjects aged 62-74 years old that were post or peri-menopausal were selected. All subjects were Caucasian with skin type I-III with moderate to severe photoaging on their forearms. The two test products were applied to mirror images in a paired comparison manner with occlusion by Fin chamber affixed with Scanpor tape. Each subject received HE on one forearm and Tr on the other forearm. The patches were changed every other day for HE for 6 applications total. Tr was applied every 3 days for 3 applications total. About 80 microliters of test product were applied to each site. On day 12, punch biopsies were collected from each test site on each subject.

The biomarker scales and definitions compared between the two topical treatments include:

Fibrillin Ab measures protein that assembles microfibrils to form elastin fibers. It uses a scale of 0=normal skin, to 3 = marked diffuse fibrillin staining.

Procollagen I immunostain measures cytoplasmic stain in dermal fibroblasts with scale of 1 = <5% positive cells to 5 = >30% positive cells.

PPAR gamma measures nuclear staining and reported as number of positive nuclei/mm^2 for keratinocyte terminal differentiation while down regulating keratinocyte proliferation.

Statistical analysis used Wilcoxon signed rank test.

Results

Safety

Despite occlusion, no adverse reactions were noted including erythema, edema, scaling with either test product.

Efficacy

As shown in Table 1. No statistically significant difference was observed between HE and Tr after measuring the two biomarkers for photoaging. However, PPAR gamma achieved a trend for statistical significance (p = 0.075) superior of HE to Tr.

Table 1: Results of Biomarker Analysis .

Biomarker	Rx	Mean Δ	s.d.	*p* value HE *vs.* Tr
Fibrillin AB:	HE	0.50	0.53	0.00
	Tr	0.50	0.53	
Procollagen2	HE	1.13	0.35	0.00
	Tr	1.13	0.35	
PPAR gamma	HE	1.75	3.62	0.075
	Tr	0.88	2.47	
N=8				
s.d.=standard deviation				
Δ=difference				

Discussion

Two bioactive markers analyzed in this trial were selected to assess the impact of these products on key structural and functional anomalies that arise early in the development of photoaging. The third biomarker must be activated to rejuvenate aged, disrupted epidermis while reversing or mitigating destructive changes induced by chronic inflammation.

Fibrillin is a glycoprotein secreted by fibroblasts into the extracellular matrix. It is incorporated into insoluble microfibrils to provide the scaffold for elastin deposition. Fibrillin is a major component of a sheath surrounding amorphous elastin. Increased Fibrillin antibody levels indicate increased synthesis of this critical protein [7].

Procollagen 2 is the initial 3-dimensional stranded structure for collagen I assembly. Its principal peptides are glycine, proline and lysine. Procollagen is modified by adding hydroxyl groups to proline and lysine. This allows for glycosylation and formation of collagen's triple helix. Procollagen is shipped from endoplasmic reticulum to Golgi apparatus then secreted into the extracellular space. This is the site of completion of formation of collagen fibrils. Increase of Procollagen 2 is one of the earliest markers indicating upregulation of collagen synthesis [8].

Peroxisome Proliferator Activated Receptor (PPAR) gamma is a nuclear receptor that regulates gene expression for lipid, glucose and amino acid metabolism. Its activation triggers keratinocyte differentiation while reducing its proliferation. It is essential for maintaining epidermal integrity for functioning skin permeability barriers by promoting in terminal differentiation. PPAR gamma also regulates skin inflammation. It is additionally critical for pilosebaceous unit homeostasis by protecting follicular epithelial stem cells. Increased levels indicate an increase in metabolic processes needed for epidermal rejuvenation and optimization [9]. The positive impact upon HE by PPAR gamma was numerically superior with a trend toward statistical significant (p = 0.08) superiority over prescription Tr 0.02%.

The limitation of this in vivo pilot study is small sample size and short duration of treatment products. These data strongly suggest a longer-duration clinical study to evaluate other biomarkers such as elastin and with a larger number of subjects (N of 36 or more) is warranted. The suggested clinical trial should include mechanical instrumentation and imaging assessments.

The test products were occluded, which increased cutaneous penetration of topically applied products from 3 to 15-fold. This accelerates reparative processes, enhancing visible results but also increases risk of adverse reactions.

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Conclusion

The unique herbal blend of HE appears to be equally effective to prescription Tr 0.02% upon biomarkers that indicate photo damage. HE appears likely to be superior to Tr in repairing the epidermis and stratum corneum .

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