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Reduction of Facial Redness With Resveratrol Added to Topical Product Containing Green Tea Polyphenols and Caffeine

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ABSTRACT

Background/Objective: Many topical formulations include antioxidants to improve the antioxidant capability of the skin. This study evaluated the ability of a unique combination of antioxidants including resveratrol, green tea polyphenols, and caffeine to reduce facial redness.
Methods: Subjects (n=16) presenting with facial redness applied the resveratrol-enriched product twice daily to the entire face. Reduction in redness was evaluated by trained staff members and dermatology house staff officers. Evaluators compared clinical photographs and spectrally enhanced images taken before treatment and at 2-week intervals for up to 12 weeks.
Results: 16 of 16 clinical images showed improvement and 13 of 16 spectrally enhanced images were improved. Reduction in facial redness continued to evolve over the duration of the study period but was generally detectable by 6 weeks of treatment. Adverse effects were not observed in any subject.
Conclusion: The skin product combination of resveratrol, green tea polyphenols, and caffeine safely reduces facial redness in most patients by 6 weeks of continuous treatment and may provide further improvement with additional treatment.

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INTRODUCTION

Facial redness can occur in association with a large number of medical problems. The most common causes of facial redness include inflammatory dermatoses, such as rosacea, perioral oral/ocular dermatitis, contact, seborrheic and atopic dermatoses and chronic sun damage. While redness is the final clinical manifestation, the biologic pathway leading to the redness may be quite varied. We refer to the common denominator in all of these as inflammation, and we now understand many molecules are involved in the inflammatory process. Many of the pathways of inflammation involve reactive oxygen species (ROS). Therefore one may conclude that molecules quenching ROS should be considered anti-inflammatory agents.

There are a number of topical formulations that include antioxidants to improve the antioxidant capability of the skin.[1,2,3,4] Two antioxidants, green tea polyphenols and caffeine, have been shown in the laboratory[5,6,7] to be very effective and have been used in a commercially available product that has been well tolerated. A third compound that has received considerable attention is resveratrol (3,5,4′-trihydroxystilbene), a polyphenolic phytoalexin found in red wines, colored berries, and peanuts.[8] Resveratrol has also been shown in the laboratory[9] to be a potent antioxidant. The myriad of clinical benefits of resveratrol led to the hypothesis that the addition of this agent to a topical preparation containing green tea polyphenols and caffeine (both of which protect skin from UV injury[10,11]) might create an even more effective skin care product. The present study demonstrates that this combination of GTP, caffeine, and resveratrol reduces facial redness.

METHODS

Stage 1

In a preliminary split-face study, volunteers applied topical antioxidant product containing green tea polyphenols and caffeine to one side of the face and the same product with resveratrol added to the other side of the face. Product was applied twice daily for 8-12 weeks. Both products were well tolerated. Facial redness was reduced on the side treated with resveratrol-enriched product (data not shown). These results led to the present study in which subjects presenting with facial redness applied resveratrol-enriched product to the entire face to evaluate the consistency of the clinically apparent reduction in redness.

Stage 2

Subjects (n = 16) presenting with facial redness applied the resveratrol-enriched product twice daily to the entire face. Reduction in redness was evaluated and photographed at 2-week intervals for up to 12 weeks. Photography was obtained by Canfield Visia Software Version 5.2.0 2010-0503a. This unit has a mode that spectrally separates the red portion of the image allowing enhanced ability to see changes in skin redness. Improvement was evaluated by nine trained staff members and 21 dermatology residents on a scale of 1 to 9. The baseline score was assigned a value of 5 for each subject. Post treatment scores lower than 5 denoted redness reduction while scores above 5 indicated an increase in redness. Evaluators compared photographs taken before treatment and at 2-week intervals for up to12 weeks. All subjects provided signed informed consent to treatment and photography.

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FIGURE 1. Clinicians (red) and trained observers (blue) independently rated clinical images of the same 16 patients. There was 100% agreement between the two groups of observers. All 16 patients exhibited signs of reduced redness after 6 weeks of treatment, based on clinical images. Note: All lines above baseline (level 5) denote improvement.

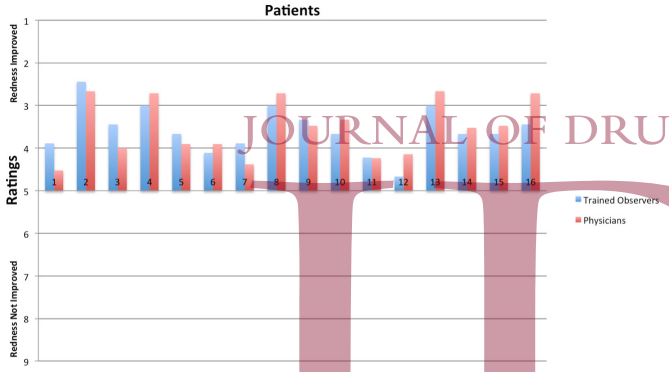
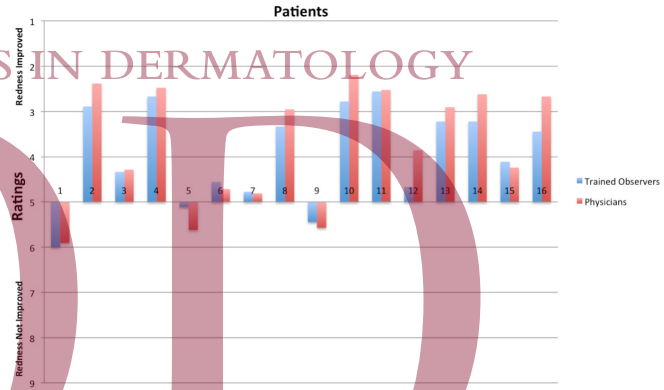


FIGURE 2. Clinicians (red) and trained observers (blue) independently rated computer-generated images of the same 16 patients. There was 100% agreement between the two groups of observers. Thirteen out of 16 patients showed reduced redness following 6 weeks of treatment, based on computer-generated images. Patients 1, 5, and 9 did not show signs of reduced redness based on computer-generated images. Note: All lines above baseline (level 5) denote improvement.



RESULTS

All subjects completed the study. Adverse effects were not observed in any subject. Two sets of images were evaluated. One set were clinical photos, the other spectrally enhanced red images that were computer generated by the Canfield software. The sets of observers evaluated the before and after images independently. During their evaluations there was no inter-observer discussion. There was 100% agreement between the groups as to which patients improved and which did not. Improvement once attained was sustained throughout the course of the study. The data suggest that 3 to 6 weeks may be sufficient time for most subjects to achieve a reduction score of 2 to 4. (Note added in proof: most of the patients have now been informally followed for more than 1 year and have maintained their improvement.)

DISCUSSION

As has been said, now that we know it works in fact, how does it work in theory? The product that reduced facial redness is a combination of a number of products produced by mother nature that each has individual histories of providing benefits by association with epidemiologic data. Uniquely these products are associated with a plethora of benefits but a noticeable absence of deleterious effects. Scientists, including our own group, have studied these molecules in test tube and animal models and drawn lots of conclusions about the nature of their activities. Discussed here are some of our favorites, but do they answer the question of how this product produces its admirable effects? Historically the first product that we evaluated clinically contained just green tea polyphenols. Note that this is was a concentrated assortment of all the molecules available from gentle extraction and concentration of the green tea leaf, intentionally not focusing on any single component as the epidemiology of benefits is for green tea and not individual components. This product was cosmetically accepted and conceptually was a potent topical antioxidant. Clinical observation suggested it had a calming effect on the users' skin, including those with inflammatory dermatoses, suggesting its anti-inflammatory nature. Our laboratory found that the addition of caffeine increased the antioxidant capacity of green tea polyphenols in a test tube model using human fibroblasts. Caffeine had already been administered topically and was being redeemed as systemically beneficial and therefore might add to the antioxidant qualities of our existing product. Back in the lab, resveratrol had proven to have antioxidant capacities and some other unique activities.[12] Guided by this laboratory data and an excellent epidemiology story, we added resveratrol producing a unique product in which all of these components were present in high concentrations in a stabilizing base. Each translation from bench top to commercial product has a period in which the older product is compared to the new for cosmetic acceptability. Everyone liked the qualities of the new product and we noticed that in those individuals with facial redness, the side treated with the resveratrol addition had reduced redness. Translational work is thought of as from the bench to the bedside but clinical observation yields facts and what remains is why.

A suggestion for the mechanism of action of this combination product centers on the concept that individual cells in an environment, in this case the skin, produce molecules that influence all the surrounding tissues and on some level the host.[13] This is now a more accepted doctrine in the cancer literature and recently in the aging literature.[14] The data presented here on redness in the skin may be explained by having the mixture of active principles in this product change how individual cells

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FIGURE 3. A 35-year-old male (skin type 2) before treatment (left) and 9 weeks after treatment with resveratrol-enriched product (right). Clinical image. Redness reduction was scored at 3.

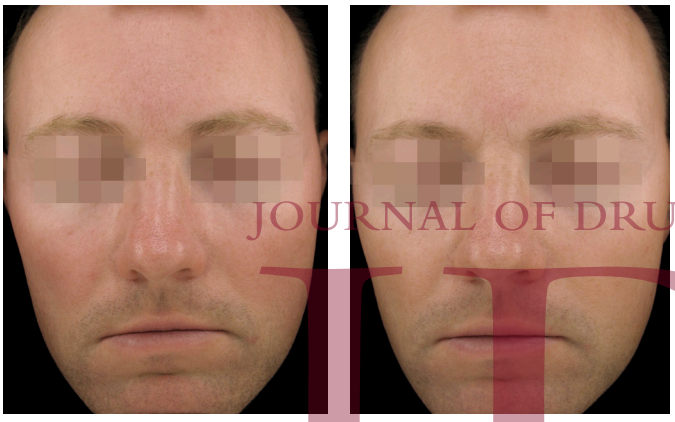
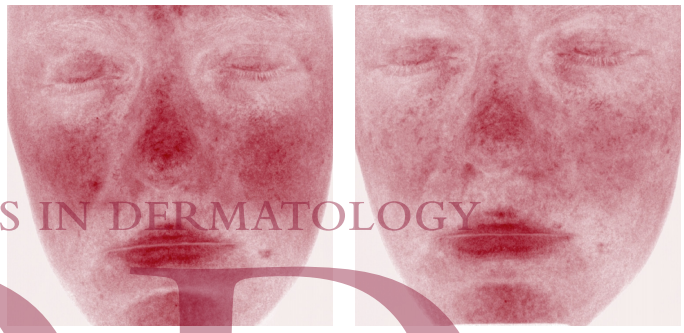


FIGURE 4. A 35-year-old female (skin type 2))before treatment (left) and 9 weeks after treatment with resveratrol-enriched product (right). Spectrally enhanced image. Redness reduction was scored at 3.



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view injury and therefore the array of molecules they produce or induce their neighbors to produce. The injured cell has at least four alternatives: complete repair, autophagy, apoptosis or necrosis. Each of these pathways has a consequence to the surrounding tissue. An example of complete repair may be the excision-repair proteins for damaged DNA that may be going on continuously without upsetting the cellular environment. Additional stress to the cell is a reactive oxygen species (ROS) assault, which could be quenched by the cell's store of antioxidants or by the exogenous antioxidants applied to the skin or consumed. This simplistic explanation needs to be expanded. Cell necrosis is the most inflammatory path for the injured cell with release of all the contents initiating myriad inflammatory pathways and immune activation. This kind of pathway probably accounts for the exacerbation of lupus after acute UV damage. Apoptosis or programmed cell death is the least inflammatory method of removing non-repairable cells as represented by the sunburn cell. The combination of resveratrol, green tea pholyphenols, and caffeine in our product proved effective in reducing redness. Each of these three compounds yields an acclamatory effect on individual cells in the surrounding environment, which may account for the observed benefits.

Green tea polyphenols (GTPs) are antioxidants shown in mice to protect against skin inflammation, associated tumorigenesis[15,16] and phototoxicity induced by psoralen plus UV-A radiation.[17] The polyphenol portion of green tea (the catechins) includes epicatechin, epicatechin-3-gallate, epigallocatechin, and epigallocatechin-3-gallate derivatives. When only the catechin portion of green tea is administered topically in mice, epigallocatechin-3-gallate (EGCG) protects best in a photocarcinogenesis model.[18] Because of this and similar models, EGCG is regarded as the most effective catechin.[19] It is important to remember that the epidemiology is for green tea and not any individual molecules. Surrogates are valid for their models. They are used for their expediency. Intentionally, the studied product uses all of the molecules in green tea leaves that would be present in the beverage on which the epidemiology is based.

Another approach to discerning mechanisms by which the combination product of the present study reduces facial redness involves pathways of inflammation. Facial redness may occur in a variety of inflammatory dermatologic disorders.[20] Since the molecular targets of each component are not identical, the components may act independently or synergistically to reduce cutaneous inflammation. All three of the components in our product have been shown to improve or protect against UV-induced skin damage. Exposure of the skin to UV radiation induces formation of ROS, which leads to inflammatory responses associated with a variety of skin disorders, including cancer. Inflammatory responses are characterized by erythema, edema, hyperplastic responses, and increases in blood vessel permeability. Both topical GTP-application and GTPs in drinking water reduce inflammation.[21] One study[22] on the anti-inflammatory component of GTPs showed that, after pretreating human skin with green tea extract and then exposing the treated area to solar-simulated light, the green tea extract inhibited UV-induced erythema in a dose-dependent manner, reduced the number of sunburn cells, and protected the epidermal Langerhans cells. Resveratrol, as a natural polyphenol, is also a pigment. This property allows it to absorb UV radiation, and when applied topically, it can reduce the penetration of UV radiation into the skin.[23] In this way, topical resveratrol acts as a natural sunscreen and reduces the inflammation and oxidative damage associated with UV exposure. Furthermore, pre-treatment of keratinocytes with resveratrol increases cell survival after these cells have been exposed to UV radiation.[24] This is also associated with a reduction in the production of ROS, and subsequent anti-inflammatory effects. Green tea phenols add to this anti-inflammatory effect. GTPs can inhibit the UV-induced infiltration of neutrophils and macrophages.[25] In our product, this effectiveness is further supplemented by caffeine. Topical caffeine has been shown to protect against UV damage in mice by eliminating UV-damaged keratinocytes,[26] and subsequently inhibiting skin

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cancer development. The topical application of caffeine to human skin provides protection from UV light via DNA repair mechanisms.[27] Caffeine has been shown to prevent or reverse UV damage by inhibiting the ataxia-telangiectasia and Rad3-related protein (ATR)-checkpoint kinase 1 (Chk1) pathway[28] involved in cell cycle control.[29] By inhibiting the ATR-Chk1 pathway, caffeine prevents tumor growth and promotes apoptosis. Lastly, should UV-damage occur, topical caffeine can eliminate UV-damaged keratinocytes[30] and subsequently inhibit skin cancer development. While this discussion frequently uses UV light as the inducer of ROS, it has been shown that both visible light and infrared also induce ROS.[31]

Our product provides a "second line" of defense in that its components also directly inhibit various inflammatory pathways. The cyclooxygenase (COX)-2 and lipoxygenase (LOX) pathways catalyze the production of pro-inflammatory substances, including prostaglandins and leukotrienes.[32,33] Various biochemical pathways are also associated with the induction of inflammatory cytokines (tumor necrosis factor-α, IL-6, and IL-1β) that stimulate the growth of tumor cells.[34] Resveratrol works to diminish inflammation by stopping COX-2 activity,[35] likely by inhibition of the protein kinase C (PKC) signal transduction suppressing COX-2 expression.[36] This finding is important because PKC is up regulated in some types of cancer.[37,38,39] Green tea phenols (GTPs) have also been shown to have an effect on the COX pathway. GTPs in drinking water reduced inflammation markers COX-2, prostaglandin E2, proliferating cell nuclear antigen, and cyclin D1 in mice with skin damage that developed after exposure to UV radiation.[40] Other studies showed that GTPs: (1) inhibit ornithine decarboxylase, COX, and LOX; and (2) inhibit release of interleukins 1, 8, 10, and 12,[41] which are all pro-inflammatory molecules. The third compound in our product, caffeine, takes yet another approach in countering inflammation. Topical caffeine inhibits cyclic AMP phosphodiesterase, which results in increased levels of cAMP in skin, which, in turn, reduces inflammatory reactions.[42,43]

Lastly, it is important to consider that an increase in cutaneous blood supply would carve a convenient pathway for inflammatory markers to reach the skin. Angiogenesis is defined as the production of new blood vessels and/or altered permeability of existing blood vessels. A key element that stimulates angiogenesis is vascular endothelial growth factor (VEGF). Resveratrol, GTPs, and caffeine down regulate angiogenesis. A study by Pietrasik and colleagues[44] demonstrated that resveratrol modulates normal somatic cells, leading to a decrease of the angiogenic activity of endothelial cells. Mesothelial cells treated with resveratrol created an angiogenesis-suppressive milieu, reflected by the inhibited proliferation and migration of endothelial cells. This suppressive effect continued even after the cells were removed from resveratrol exposure. Endothelial cells treated directly with resveratrol also showed anti-angiogenic activity. The anti-angiogenic effect of resveratrol may be associated with its activation of glycogen-synthase kinase 3b (GSK3b), which results in decreased production of VEGF via down-regulation of b-catenin.[45] GTPs play an anti-angiogenic role by inhibiting phosphorylation of VEGF receptors[46] required for VEGF binding. Meanwhile, pretreatment of cells with caffeine significantly reduces adenosine-induced VEGF promoter activity and VEGF and IL-8 expression.[47] The anti-angiogenic effects of all three compounds in our product may directly reduce redness.

CONCLUSION

The skin product's unique combination of resveratrol, green tea polyphenols, and caffeine reduces facial redness in most patients after 3 to 6 weeks of continuous treatment and may provide further improvement with additional treatment.

DISCLOSURE

The study was initiated and funded by one of the authors (N.I.B.). That author contributed to the conceptualization and design of the product but holds no patents and does not benefit from its sale. This product is commercialized as Replenix Power of Three by Topix Pharmaceuticals.

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