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

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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 and rashes include inflammatory dermatoses, infections, and connective tissue disorders. Rosacea is associated with flushing, erythema, telangiectasia, papules, and pustules. Its etiology is unknown. Perioral ocular dermatitis is an erythematous eruption of unknown etiology while atopic dermatitis, an inflammatory skin disease, frequently affects the cheeks in infants and other facial areas in adults. Contact dermatitis, seborrheic dermatitis, psoriasis, cellulitis, discoid lupus erythematosus, dermatomyositis, and impetigo are also associated with facial redness *Tavadia 2003). Chronic sun damage, genetic flusher-blusher, and acne are also frequently encountered.

While redness is the final clinical manifestation, the pathophysiology 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). It is probably true quenching ROS, should be considered an anti-inflammatory agent.

Many topical formulations include antioxidants to improve the antioxidant capability of the skin (Berson 2008, Farris 2007, Palmer 2010). An antioxidant that has received considerable attention is resveratrol (3,5,4′-trihydroxystilbene), a polyphenolic phytoalexin found in red wines, colored berries, and peanuts (Baxter 2007).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 [Elmets 2001, Heffernan 2009]) might be an even more effective skin care product. The present study evaluated the ability of a resveratrol-enriched product containing green tea polyphenols and caffeine to reduce facial redness in human skin.

Methods

Stage 1. In a preliminary split-face study, 16 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 12 weeks. Both products were well tolerated. After 12 weeks subjects with facial redness showed a reduction in redness 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 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 9 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 house staff residents on a scale of 1 to 9. The baseline score was assigned a value of 5 for each subject. Posttreatment 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 to 9 weeks. All subjects provided signed informed consent to treatment and photography.

Results

All subjects completed the study. Adverse effects were not observed in any subject. Data were analyzed by non-parametric statistics because the 9-point scale is not continuous and scoring data were not normally distributed as shown by the Shapiro-Wilk test.

As shown in Figure 1, the collective data show that median redness scores ranged from 2 to 6 and that most subjects (69%-99%) achieved a redness reduction of at least 1 score level at the end of their treatment period. Redness in the remaining subjects (0%-31%) either did not change (0%-19%) or increased by 1 score value (0%-19%).

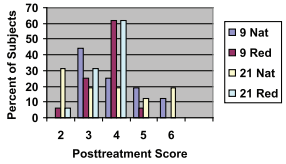

Figure 1. Median posttreatment score vs. percentage of subjects for four sets of data. Baseline score was set at 5 for each subject. Posttreatment scores less than 5 indicated reduced redness while scores greater than 5 denoted increased redness.

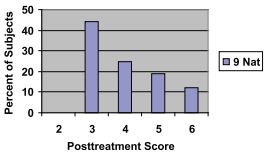

Figure 2. Graph of 9 evaluators-natural photo data.

A 75-year-old female (skin type 2) before treatment (left) and 4 weeks after treatment with resveratrol-enriched product (right). Redness reduction was scored at 3.

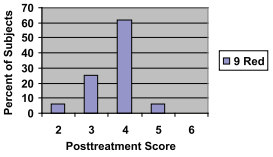

Figure 3. Graph of 9 evaluators-redness photo data.

A 72-year-old male (skin type 2) before treatment (left) and 9 weeks after treatment with resveratrol-enriched product (right). Redness reduction was scored at 3.

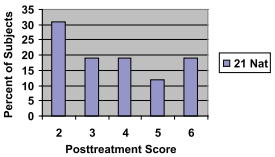

Figure 4. Graph of 21 evaluators-Natural photo data

A 27-year-old female (skin type 1))before treatment (left) and 5 weeks after treatment with resveratrol-enriched product (right). Redness reduction was scored at 3.

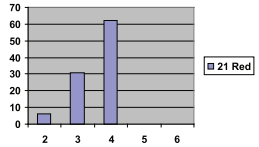

Figure 5. Graph of 21 evaluators- redness photo data.

The possible role of treatment duration on facial redness reduction was also evaluated for each of the four data sets (Table 1). For the 3 to 6-week treatment period the proportions of subjects among the four data sets did not differ significantly by Pearson's chi-square test (p = 0.1967). A similar result (p = 0.1059) was obtained when the 7 to 9 week treatment period data were compared. These results indicate that for each of the four sets of data, the distribution of subjects among median scores did not differ significantly within each of the two treatment periods.

Table 1. Distribution of subjects among median scores for the 3 to 6 and 7 to 9-week treatment periods for each of the four data sets

Median Score	Weeks of Treatment							
	3 to 6				7 to 9			
	9 Nat	9 Red	21 Nat	21 Red	9 Nat	9 Red	21 Nat	21 Red
2	0	1	4	1	0	0	1	0
3	6	4	3	5	1	0	0	0
4	4	7	2	6	0	3	1	4
5	1	0	2	0	2	1	0	0
6	1	0	1	0	1	0	2	0
	X^2 = 15.88, df = 12, p = 0.1967 (ns)				X^2 = 18.33, df = 12, p = 0.1059 (ns)			

The distributions of subjects among the median scores for the 3 to 6-week treatment period were compared with those for the 7 to 9-week treatment period for each of the four data sets. As shown in Table 2, differences in proportions of subjects for the 3 to 6 and 7 to 9-week treatment durations did not achieve statistical significance for any of the four data sets.

Table 2. Comparisons of distributions of subjects among median scores for the 3 to 6 and 7 to 9-week treatment periods

Median Score	9* Nat		9* Red		21* Nat		21* Red	
	3-6†	7-9†	3-6†	7-9†	3-6†	7-9†	3-6†	7-9†
2	0	0	1	0	4	1	1	0
3	6	1	4	0	3	0	5	0
4	4	0	7	3	2	1	6	4
5	1	2	0	1	2	0	0	0
6	1	1	0	0	1	2	0	0
	P = 0.1573 (ns)		P = 0.1870 (ns)		P = 0.3283 (ns)		P = 0.2019 (ns)	

*No. of evaluators.
†Weeks of treatment.
Nat = natural photos; red = red images.

Discussion

Overall, the results suggest that the treatment effect (i.e., reduction in facial redness) requires up to 6 weeks of treatment for most subjects. It is possible that subjects achieving redness reduction in 3 to 6 weeks may improve further. However, if redness has not been reduced after 6 weeks of treatment, it is unlikely that further treatment will reduce redness. Clinical examples are presented in Figures 2-4.

Many topical formulations include antioxidants. Common examples include the polyphenols (found in tea), vitamin C, vitamin E, silymarin, and soy isoflavones (Pinnell 2003). Interest in resveratrol became stronger when, in 1997, resveratrol was shown to have cancer chemopreventative effects in tumor initiation, promotion, and progression stages in humans (Jang 1997). Resveratrol has since been shown to reduce intracellular hydrogen peroxide-upregulated ROS in human fibroblasts in vitro (Jagdeo 2010), modulate genetic expression (Baxter 2007), inhibit inflammatory mediators (Baxter 2007), prevent skin cancer (Aziz 2005), exhibit antiproliferative activity in multiple forms of cancer (Athar 20078, Ding 2002), promote apoptosis in tumor cells (Delmas 2003), improve dermal wounds (Khanna 2002, Sen 2002, Khanna 2001), inhibit UVB-induced skin damage (Afaq 2003), and protect against LDL oxidation (Brito 2003). Resveratrol has also been shown to have antifungal and antibacterial properties (Chan 2002) and to reduce levels of ROS in HaCaT keratinocytes exposed to UVA light (Baxter 2007).

Green tea polyphenols (GTPs) are antioxidants shown in mice to protect against skin inflammation and tumorigenesis (Mukhtar 1994, Katiyar 2000) and phototoxicity induced by psoralen plus UV-A radiation (Zhao 1999). GTPs (catechins) include (—) epicatechin, (—) epicatechin-3-gallate, (—) epigallocatechin, and (—) epigallocatechin-3-gallate derivatives. When administered topically in mice, (-)-epigallocatechin-3-gallate protects against photocarcinogenesis (Gensler 1996) and is regarded as the most effective catechin.

Topical caffeine has been shown to protect against UV damage in mice by eliminating UV-damaged keratinocytes (Koo 2007) and subsequently inhibiting skin cancer development. Topical caffeine has also been to inhibit formation of galactose cataracts (Varma 2010) and improve psoriasis vulgaris (Vali 2005).

Exposure of the skin to UV radiation induces inflammatory responses associated with a variety of skin disorders, including cancer. Regarded as early events in tumor promotion, development, or both, inflammatory responses are characterized by erythema, edema, hyperplastic responses, and increases in blood flow blood vessel permeability, and levels of COX-2 and prostaglandin. These responses are also associated with the induction of inflammatory cytokines (tumor necrosis factor-α, IL-6, and IL-1β) (Meeran 2009).

It is useful to summarize mechanisms by which the combination product of the present study reduces facial redness and inflammation. Facial redness may occur in a variety of inflammatory dermatologic disorders and an effective treatment of facial redness without the side effects of steroids would be useful (Oh 2010). Since the molecular targets of each component are not identical, the components may act independently and synergistically to reduce cutaneous inflammation.

Conclusion

The skin product 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.

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