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Research Article

Mitigating Visible Light and Long Wavelength UVA1-induced Effects with Topical Antioxidants

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ABSTRACT

The role of topical antioxidants (AOs) on visible light plus ultraviolet A1 (VL+UVA1)-induced skin changes were evaluated. Twenty subjects with skin phototypes (SPTs) I–VI had placebo and concentrations of an AO blend applied to their back (AO 0.5%, 1.0% and 2.0%). Treated and control sites were irradiated with VL+UVA1. Colorimetric and diffuse reflectance spectroscopy (DRS) assessments were performed immediately, 24 h and 7 days after irradiation. Subjects with SPT I–III had erythema that faded within 24 h, while SPT IV–VI had persistent pigmentation. SPT I–III demonstrated significantly less erythema at the 2% AO site while SPT IV–VI demonstrated significantly less immediate pigmentation at 2% AO site and less pigmentation (approaching significance, $P = 0.07$) on day 7 compared with control. Immunohistochemistry from biopsies of 2% AO and placebo at 24 h did not demonstrate a significant change in COX-2 or MART-1 for any SPT. There was a decrease in cyclin D1 for SPT IV–VI which was approaching significance ($P = 0.06$) but not for SPT I–III. The results indicate that topical AO inhibits erythema in SPT I–III and reduces pigmentation in SPT IV–VI caused by VL+UVA1. AO may help prevent worsening of pigmentary disorders and should be incorporated into photoprotection.

INTRODUCTION

Visible light (VL; 400–700 nm) has been demonstrated to cause sustained pigmentation (1–5). Additionally, a small amount of long-wavelength ultraviolet A1 radiation (UVA1, <4%) in combination with VL, (VL+UVA1, 370–700 nm) has a synergistic effect on pigmentation and erythema (6). This has implications for pigmentary disorders such as postinflammatory hyperpigmentation and melasma. The majority of currently available sunscreen products provide inadequate protection against

VL+UVA1-induced effects. This is concerning since the skin is exposed to these wavelengths when outdoors.

While ultraviolet B (UVB) radiation causes direct DNA damage and erythema/sunburn by directly inducing cyclobutane pyrimidine dimers, longer wavelengths such as UVA are poorly absorbed by DNA and instead indirectly cause DNA damage by generating reactive oxygen species (ROS) after absorption by flavins, porphyrins and other chromophores (7–11). A wide variety of stimuli and metabolic processes generate ROS, which strip electrons from other molecules (oxidation) and generate more ROS in a self-propagating chain reaction. This excess production of oxidizing molecules is termed oxidative stress and leads to the damage of lipids, proteins and nucleic acids. ROS and oxidative stress are implicated in sunburn, carcinogenesis, inflammatory diseases and aging. Oxidative stress also contributes to pigmentation (12). Alpha-melanocyte stimulating hormone (α -MSH), a major stimulus of melanogenesis, reduces UV-induced hydrogen peroxide levels in irradiated melanocytes, further supporting the link between pigmentation and oxidative stress (13). DNA damage from solar radiation also stimulates melanogenesis, and DNA repair is induced alongside pigmentation (11). Moreover, short wavelength VL also upregulates melanogenesis through G-protein-coupled membrane receptor opsin-3 (14). Since a possible mechanism of VL+UVA1-induced effects is oxidative stress, targeting ROS, such as superoxide, hydroxyl radical and singlet oxygen, may potentially mitigate the effects of VL+UVA1.

AOs are molecules that scavenge free radicals and terminate the chain reactions that propagate ROS. Solar radiation is known to deplete endogenous AO including glutathione, tocopherol and ubiquinone (9). AO combinations using ingredients such as feverfew extract, soy extract and tocopherol can halve visible light-induced ROS induction (9). Other AO such as mannitol can inhibit photo-oxidative damage from UVB (15). The combination of diethylhexyl syringylidene malonate and vitamin E have been shown to be effective in suppressing the formation of ROS induced by UVA and UVB at 0.9% and 0.5%, respectively, when added in sunscreen formulations and evaluated by two-photon fluorescence microscopy (16). This data suggests a potential role for AO to mitigate pigmentation induced by VL+UVA1.

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However, there are limited studies regarding AO prevention of either UV or VL-induced pigmentation. In this study, varying concentrations of an AO product (Table 1) were tested for their ability to mitigate VL+UVA1-induced pigmentation and erythema.

MATERIALS AND METHODS

Twenty subjects (12 males, 8 females), 10 with Fitzpatrick skin phototype (SPT) I-III (0 SPT I, 9 SPT II, 1 SPT III) and 10 with SPT IV-VI (3 SPT IV, 7 SPT V, 0 SPT VI), were enrolled. The study was approved by the Institutional Review Board at Henry Ford Hospital and performed at Henry Ford Hospital. Informed consent was obtained from all subjects. All guidelines from the Declaration of Helsinki, good clinical practice (GCP), and international conference on harmonization (ICH) were followed. Subjects had all avoided excessive sun exposure for one month prior to participating in the study. Subjects who had photo-aggravated conditions or photodermatoses, a history of skin cancer or a history allergy to sunscreens or topical products were excluded from the study. Those who were on photo-sensitizing medications, pregnant or breastfeeding were also excluded. All subjects stated a willingness to avoid intentional sun exposure for the duration of the study. Subjects did not use any topical or systemic products which could interfere with the assessments during the course of the study.

A modified solar simulator was utilized: Solar Light LS1000 with xenon arc lamp and customized filters (Solar Light Company Inc, Glen-side, PA), filtered spectral output consisting of 2.0% UVA1 (340–400 nm), 97.3% VL (400–700 nm) and 0.7% Infrared (700–1600 nm) (Fig. 1) (17). Table 1 shows the AO blend topical formulations containing variable concentrations of a singlet oxygen quencher (diethylhexyl syringylidene malonate) and fixed concentrations of vitamins used in this study.

On day 0, small areas of the subjects' backs were occluded for 1 h with different concentrations of the AO blend: 0.5%, 1.0%, 2.0%, a duplicate 2.0% site for biopsy and placebo. These sites, as well as untreated sites, were then irradiated with 480 J cm⁻² of VL+UVA1 in the SPT I-III group and 320 J cm⁻² in the SPT IV-VI group at an irradiance of approximately 86 mW cm⁻². These doses have previously been established to be the minimum necessary to induce sustained erythema and pigmentation in their respective SPTs (6).

Investigator Global Assessment scores (IGA), colorimetric and spectroscopic (DRS) assessments were performed immediately, at 24 h and 7 days after irradiation (6). IGA scoring (Table 2) was performed by a blinded single grader. For the colorimetry measurements, Δa parameter, herein referred to as relative erythema, was used to assess erythema and the change in individual typology angle (ΔITA) was used to assess pigmentation. For DRS, the overall darkness of the site was assessed as relative pigment. This was calculated via the area under the curve (AUC) of the differential apparent absorbance spectra between 400 and 700 nm (18).

In addition, 4-mm punch biopsies were obtained 24 h after irradiation from sites treated with placebo and 2% AO. Inflammation, cell

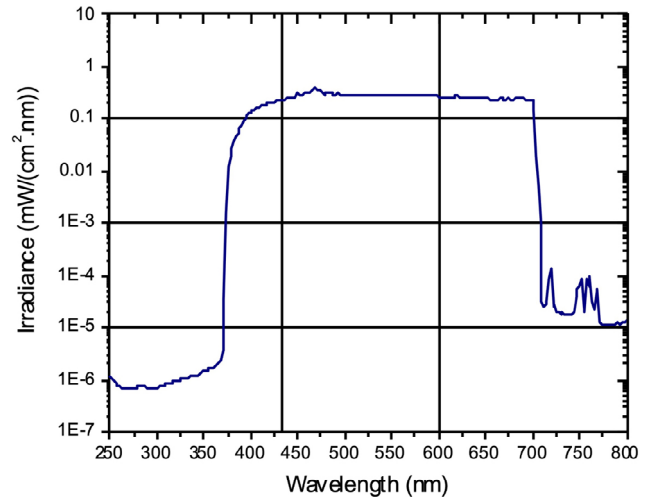


Figure 1. Spectral output of the solar simulator.

Table 2. Investigator's Global Assessment (IGA) scores.

IGA	Description for hyperpigmentation	Description for erythema
0	Clear of hyperpigmentation	Clear of erythema
1	Almost clear of hyperpigmentation	Almost clear of erythema
2	Mild, but noticeable hyperpigmentation	Mild, but noticeable erythema
3	Moderate hyperpigmentation (medium brown in quality)	Moderate erythema (pink in quality), no sharp borders
4	Severe hyperpigmentation (dark brown in quality)	Severe erythema (dark pink in quality), sharp borders
5	Very severe hyperpigmentation (very dark brown, almost black in quality)	Very severe erythema (very dark pink, almost red in quality)

proliferation and melanocyte count of formalin-fixed, paraffin-embedded tissue sections were compared by counting cells staining positively for cyclooxygenase-2 (COX-2), cyclin D1 and MART-1, respectively. Slides were examined using an Olympus BX51 microscope at 40x magnification. MART-1-staining cells were counted across five 40x fields. COX-2 and cyclin D1-staining cells were counted in three 40x fields. Nuclear cyclin D1 staining and red cytoplasmic COX-2 staining were considered positive.

Data analysis was done separately for subjects with SPT I-III and those with SPT IV-VI. Within each SPT group, the primary analysis was to compare the erythema and hyperpigmentation scores as well as colorimetry and DRS results between the untreated site and each of the three treated sites using paired t-tests with the Hochberg multiple comparison methodology. For the three comparison results, the smallest *P*-value would be significant if it was less than 0.0167, the middle *P*-value would be significant if it was less than 0.0333 and the largest *P*-value would be significant if it was <0.05.

RESULTS

VL+UVA1-induced erythema, particularly in SPT I-III subjects, was most intense immediately after irradiation and faded within 24 h (Fig. 2a). This group did not develop as much pigmentation as the SPT IV-VI group at any time point. Subjects with SPT IV-VI had intense pigmentary responses to VL+UVA1 with the

Table 1. AO blend composition.

	AO Blend Placebo	AO Blend 0.5%	AO Blend 1%	AO Blend 2%
Ingredients				
Diethylhexyl Syringylidene Malonate, Oxyxex ST [®]	–	0.50%	1.00%	2.00%
Vitamin E, USP	–	0.25%	0.25%	0.25%
C12 15 Alkyl Benzoate, Tegosoft TN2 [®]	50.00%	50.00%	50.00%	50.00%
Ascorbyl Palmitate NF	–	0.01%	0.01%	0.01%
Alcohol SD 40-B	40.00%	39.24%	38.74%	37.74%
Propylene Glycol, USP	10.00%	10.00%	10.00%	10.00%
Total	100.00%	100.00%	100.00%	100.00%

most intense response observed immediately after irradiation (immediate pigment darkening) (Fig. 2b).

For subjects with SPT I-III, Fig. 3a–c represents average IGA scores for erythema, colorimetry-measured Δa and DRS-measured AUC, respectively, performed immediately after VL+UVA1 irradiation. Colorimetry Δa and DRS-measured AUC demonstrated that sites treated with 2% AO had significantly less erythema compared with untreated control (Fig. 3b,c). The 2% AO sites also had less erythema by IGA scores, however statistical significance was not reached (Fig. 3a). Figure 3d–f represents average IGA scores for pigmentation, colorimetry-measured ΔITA and DRS-measured AUC performed 7 days after VL+UVA1 irradiation in SPT I-III subjects. As seen in Fig. 3d, very mild clinical pigmentation was observed. That said, objective instrumental assessment did capture pigment formation. The ΔITA demonstrated that sites treated with 1% and 2% AO had less pigmentation relative to the untreated control, although statistical significance was not reached, but was approaching ($P = 0.09$ for 1% AO blend and $P = 0.08$ for 2% AO blend, Fig. 3e). DRS measured AUC, which accounts for overall darkness, demonstrated that 2% AO sites were statistically significantly lighter compared with untreated control (Fig. 3f).

For subjects with SPT IV-VI, Fig. 4a–c represents IPD evaluations as assessed by average IGA scores for pigmentation, colorimetry-measured ΔITA and DRS-measured AUC, respectively, performed immediately after irradiation with VL+UVA1. Sites treated with 2% AO had less IPD relative to untreated control (Fig. 4a–c). A statistically significant difference was observed for colorimetry-measured ΔITA values (Fig. 4b) but not for clinical IGA scores for pigmentation and DRS measured AUC. Figure 4d–f represents delayed tanning (DT) evaluations as assessed by average IGA scores for pigmentation, colorimetry-measured ΔITA and DRS-measured AUC performed 7 days after VL+UVA1 irradiation in SPT IV-VI subjects. The colorimetry-measured ΔITA for the sites treated with 2% AO blend was approaching significance ($P = 0.07$) when compared with the untreated control. There was no statistically significant

difference in pigmentation for IGA scores and DRS-measured AUC for pigmentation between untreated control and AO treated sites.

There were no significant differences observed on immunohistochemical analysis of placebo and 2% AO blend treated biopsy sites 24 h after irradiation in all SPT for COX-2 and MART-1 staining (Fig. 5). Of note, the immunochemical analysis of placebo and 2% of AO blend-treatment for Cyclin D1 was approaching significance ($P = 0.06$) for SPT IV-VI. This trend in cyclin D1 was not observed for SPT I-III (Fig. 5).

DISCUSSION

The VL+UVA1 doses used in this study, 480 and 320 J cm⁻², correspond to approximately 2.5 and 1.5 h of outdoor sun exposure, respectively (17). The DRS and colorimetry data demonstrated that the 2.0% AO blend concentration provided protection against VL+UVA1-induced immediate erythema and delayed pigmentation in light-skinned individuals (SPT I-III). The colorimetry ΔITA data also indicated that 2.0% AO provided some protection against VL+UVA1-induced immediate and delayed pigmentation in the melanocompetent group (SPT IV-VI). Melanocompetent refers to having melanin to protect against sun damage. Conditions including postinflammatory hyperpigmentation and melasma are common in light skinned and melanocompetent groups and can be worsened by sun exposure. In addition, other dermatologic conditions can be triggered or exacerbated by exposure to VL and/or UVA1 including cutaneous porphyrias, solar urticaria and chronic actinic dermatitis (19). Thus, photoprotection is an important part of management in these patients.

The fact that VL+UVA1 causes pigmentation and may cause oxidative DNA damage reveals limitations in current photoprotection strategies. None of the currently available organic UV filters listed in FDA monograph protects against VL (20). While pigmentary grade inorganic filters (titanium dioxide and zinc oxide) provide protection against VL, they are not widely used in sunscreen products as they leave noticeable white residue on

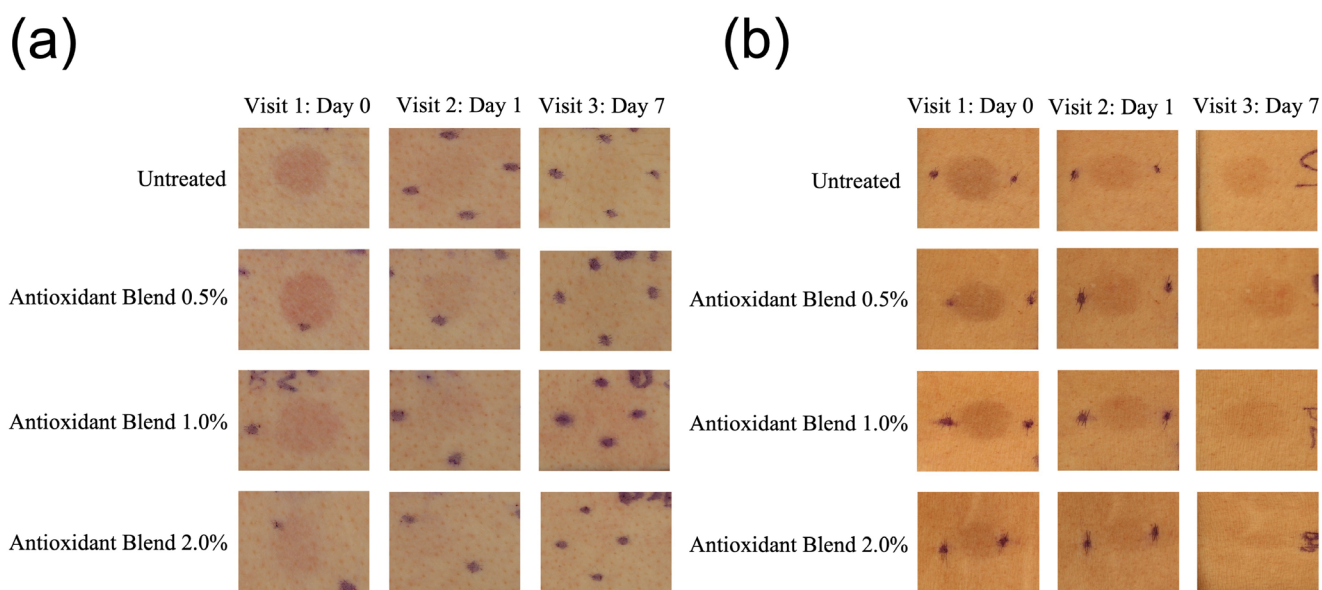


Figure 2. Photographs of sites immediately, 24 h and 7 days after VL+UVA1 irradiation for subjects with (a) SPT I-III and (b) SPT IV-VI.

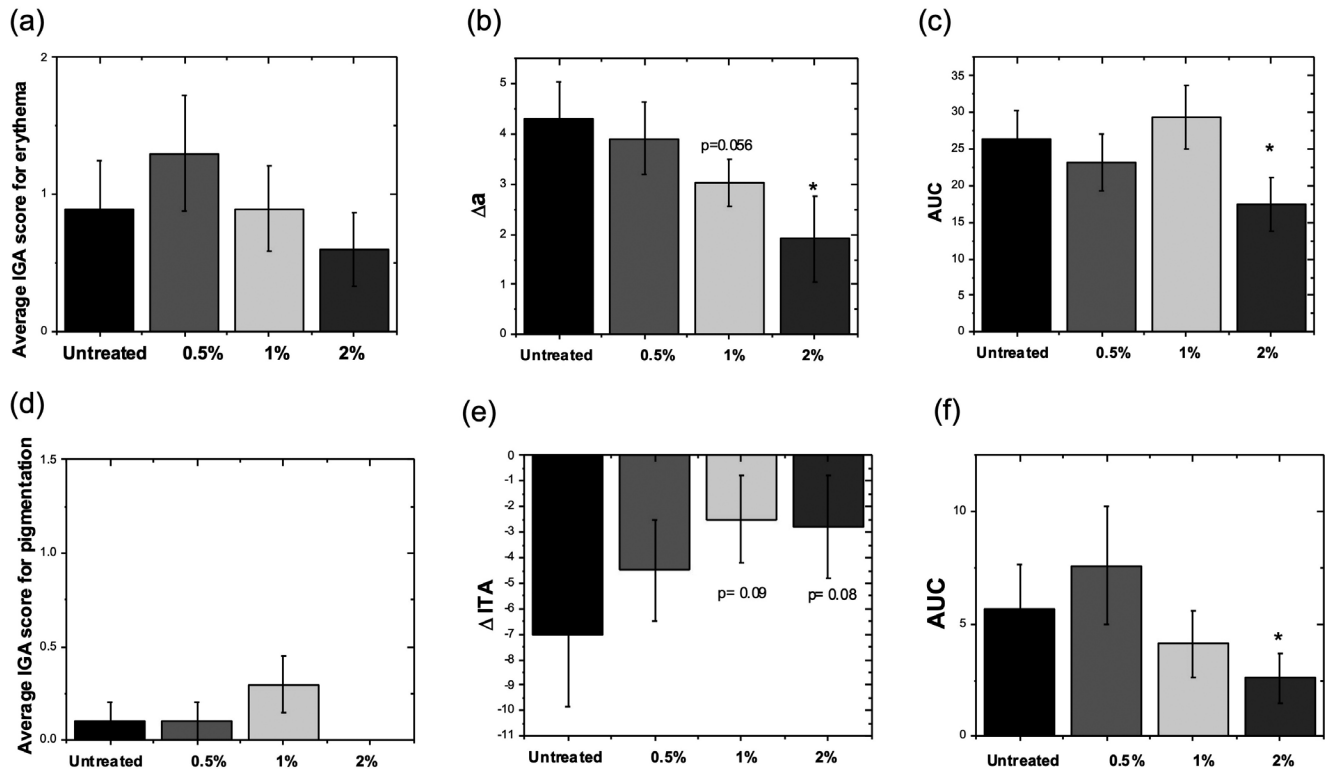


Figure 3. Erythema and pigmentation in SPT I-III subjects. Average IGA scores for erythema (a), colorimetry-measured relative erythema (b) and DRS-measured AUC (c) immediately after VL+UVA1 irradiation. Average IGA scores for pigmentation (d), colorimetry-measured ΔITA (e) and DRS-measured AUC (f) 7 days after VL+UVA1 irradiation.

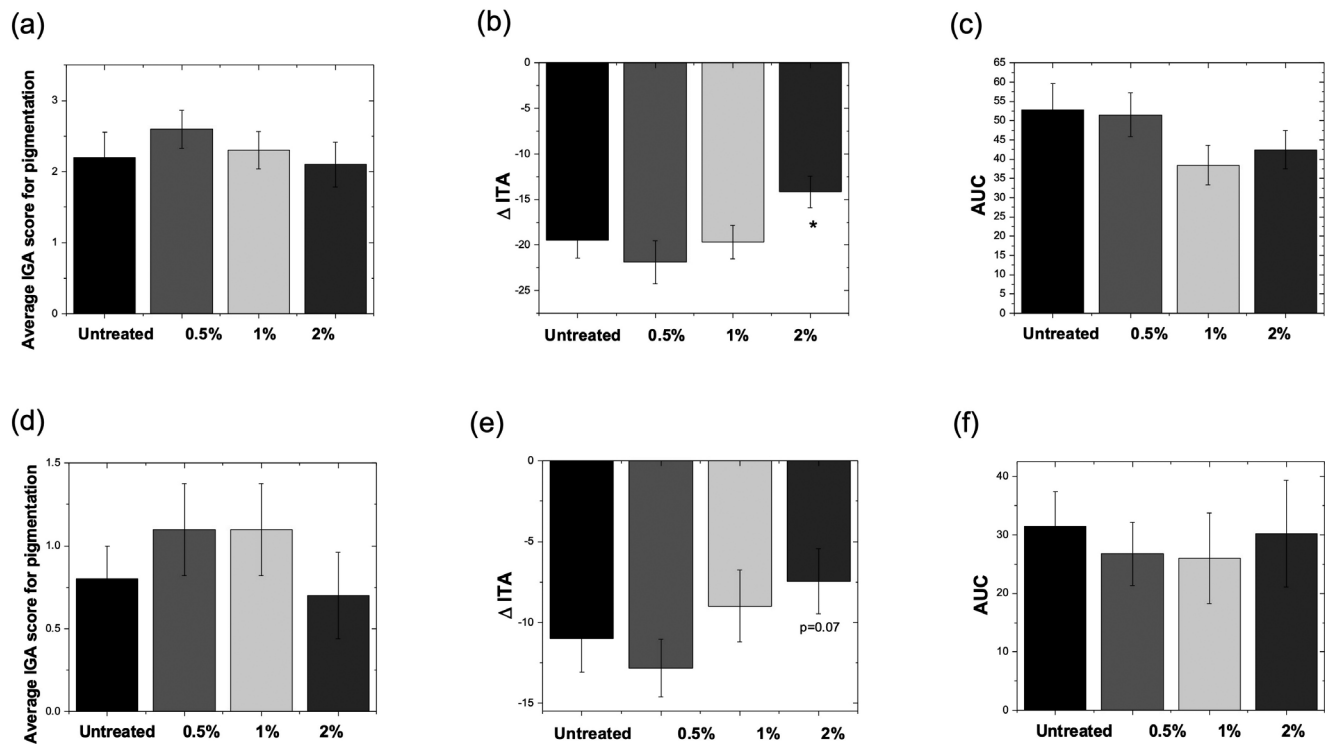


Figure 4. Immediate pigmentation and delayed tanning in SPT IV-VI subjects. Average IGA scores for pigmentation (a), colorimetry-measured ΔITA (b) and DRS-measured AUC (c) immediately after VL+UVA1 irradiation. Average IGA scores for pigmentation (d), colorimetry-measured ΔITA (e) and DRS-measured AUC (f) 7 days after VL+UVA1 irradiation.

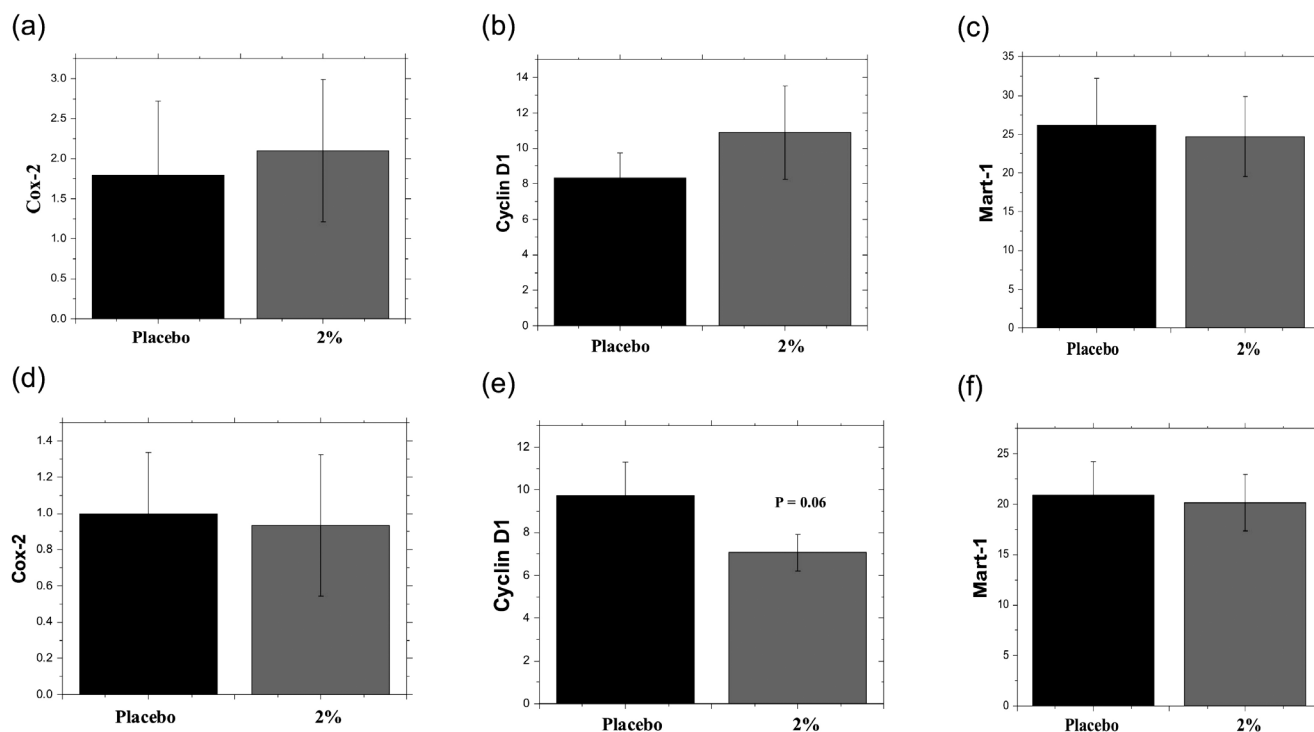


Figure 5. Immunohistochemical staining results. No significant differences observed in (a) COX-2, (b) cyclin D1 and (c) MART-1 between placebo and 2% AO blend 24 h after irradiation for those with SPT I-III. No significant differences observed in (d) COX-2 and (f) MART-1, while (e) cyclin D1 was approaching significance ($P = 0.06$) between placebo and 2% AO blend 24 h after irradiation for those with SPT IV-VI.

the skin. Inorganic filters are most commonly incorporated into the final products as nanosized particles to improve the cosmesis; however, because of their small diameters, they do not reflect visible light (18,19). Currently, the only available sunscreens that have the potential to down-regulate VL-induced skin changes are tinted sunscreens. These sunscreens contain iron oxides (listed as inactive ingredients), or pigmentary titanium dioxide, all reflect VL (19).

Recent studies have explored other topical and oral AO against UV as well as VL-induced photodamage. Licochalcone A (LicA), extracted from the roots of *Glycyrrhiza inflata*, has been identified as very potent AO which inhibits UV-induced ROS generation, activates NRF2 in primary human fibroblasts, and has a protective effect on cutaneous carotenoids *in vivo* (20).

Carotenoids, which are available orally and topically, help prevent free radical formation, inflammation and pigment deposition through tyrosinase inhibition (21). A randomized, double-blind, placebo controlled clinical trial in 46 subjects using an oral carotenoid vs placebo for 12 weeks demonstrated statistically significantly less erythema post UV irradiation in the oral carotenoid group compared to placebo (21).

Polyphenols are another class of AO which scavenge free radicals and inhibit tyrosinase-catalyzed oxidation (22, 23). Green and white tea, and pomegranate extract all contain polyphenols. Oral and topical administration of green tea has been shown in mouse models to protect against UV-induced carcinogenesis (24). Several studies of topical green tea have also shown protection against UV-induced damage in humans by way of prevention of UV-induced erythema, generation of ROS, damage to Langerhans cells and formation of cyclobutane pyrimidine dimers (25–28). Administration of oral green tea has also shown

reduction in UV-induced erythema in humans (29). Similarly, a study in which 13 subjects received oral pomegranate extract containing polyphenols compared with placebo found that there was a statistically significant reduction in pigmentation in the polyphenol treatment group after UV irradiation when compared with placebo (30).

The impact of oral *Polypodium leucotomos* extract (PLE) was recently evaluated against VL effects. PLE contains polyphenols and has been shown to reduce oxidative stress, inflammation and DNA damage via prevention of membrane-lipid peroxidation, reducing glutathione oxidation and quenching free radicals following UVA and UVB irradiation in mice, *ex vivo* and *in vivo* (31,32). Twenty-two subjects underwent VL irradiation prior to PLE administration and were followed for 7 days to assess baseline response (33). VL irradiation was performed on the contralateral side of the subject's back after 28 days of PLE supplementation. Pre- and post-PLE responses demonstrated no difference in clinical assessments; however, instrumental assessments suggested a statistically significant decrease in pigment formation (33).

While the studies discussed above evaluated oral AO supplements and explored the effects of UV irradiation alone or VL alone, this study investigated the impact of topical AO on the synergistic effects of VL plus long wavelength UVA1. As the data in this study shows, the concentration of AO must be sufficient to have a significant effect. Limitations of this study include a relatively small sample size, investigation of only the AO in this product, limited information on how the product affects biologic pathways and limited information regarding optimal biopsy timeline acquisition. Future studies should test full formulation products to assess for efficacy and protection.

Results of this study cannot be generalized to all AO blends on the market. Different AO blends could have different properties and will need to be evaluated prior to claiming any protection. Future areas of research should also include comparing the *in vivo* effectiveness of fully formulated product with investigated AO as an ingredient, and efficacy evaluation of different AO/sunscreen combinations to real world situations.

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