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ORIGINAL ARTICLE

# Evaluation of efficacy of antioxidant-enriched sunscreen prodcuts against long wavelength ultraviolet A1 and visible light

**Eduardo Ruvolo**[1] | **Wyatt Boothby-Shoemaker**[2,3] | **Nishant Kumar**[4] | **Iltefat H. Hamzavi**[2] | **Henry W. Lim**[2] | **Indermeet Kohli**[2,5]

[1]Beiersdorf Inc., Florham Park, New Jersey, USA

[2]Photomedicine and Photobiology Unit, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan, USA

[3]Michigan State University College of Human Medicine, East Lansing, Michigan, USA

[4]College of Literature, Science and Arts, University of Michigan, Ann Arbor, Michigan, USA

[5]Department of Physics and Astronomy, Wayne State University, Detroit, Michigan, USA

**Correspondence**
Indermeet Kohli, Ph.D. Photomedicine and Photobiology Unit, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan, USA.
Email: ikohli1@hfhs.org

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Beiersdorf Inc

## Abstract

**Objective:** The synergistic effects of VL and long wavelength UVA1 (VL + UVA1, 370–700 nm) on inducing pigmentation and erythema in skin have been demonstrated and linked to exacerbation of dermatologic conditions including melasma and post-inflammatory hyperpigmentation. This study aimed to compare the photoprotection of organic sunscreens enriched with antioxidant (AO) combinations against VL + UVA1 induced biologic effects. The efficacy was compared with that offered by a commercially available tinted sunscreen.

**Methods:** Ten healthy adult subjects with Fitzpatrick skin phototypes IV–VI were enrolled (nine completed). VL + UVA1 dose of 380 J/cm$^2$ was utilized. Assessment methods were polarized photography, investigator global scoring and diffuse reflectance spectroscopy (DRS). Measurements were obtained at baseline and immediately, 24 h and 7 days after irradiation.

**Results:** Sites treated with tinted sunscreen product had significantly less pigmentation compared with untreated but irradiated skin at all time points. However, DRS results demonstrated that the 5-AO sunscreen performed comparably or better than all sunscreens tested with relatively lower dyschromia, delayed erythema and pigmentation.

**Conclusion:** These results highlight the potential of AO-enriched sunscreens to be photoprotective against VL + UVA1. The combination of efficacy and the cosmetic appearance of this product may provide wider acceptability which is crucial considering the limited available means of protection against this waveband.

KEYWORDS

antioxidants, hyperpigmentation, melanogenesis, suncare/UV protection, visible light

Eduardo Ruvolo and Wyatt Boothby-Shoemaker contributed equally to this work.

**Résumé**

**Objectif:** les effets synergiques de la lumière visible (LV) et des rayons ultraviolets long (UVA1) (LV + UVA1, 370 à 700 nm) sur l'induction de la pigmentation et de l'érythème cutané ont été démontrés et liés à l'exacerbation des affections dermatologiques, notamment le mélasma et l'hyperpigmentation post-inflammatoire. Cette étude visait à comparer la photoprotection des écrans solaires organiques enrichis en associations antioxydantes (AO) contre les effets biologiques induits par LV+UVA1. L'efficacité a été comparée à celle offerte par un écran solaire teinté disponible dans le commerce.

**Méthodes:** dix sujets adultes en bonne santé présentant des phototypes cutanés de Fitzpatrick IV à VI ont été inclus (neuf ont terminé l'étude). On a utilisé une dose LV+UVA1 de 380 J/cm2. Les méthodes d'évaluation étaient la photographie polarisée, le score global de l'investigateur et la spectroscopie de réflectance diffuse (DRS). Les mesures ont été obtenues immédiatement à l'entrée dans l'étude et, 24 h et 7 jours après l'irradiation.

**Résultats:** les sites traités avec un produit de protection solaire teinté présentaient une pigmentation significativement inférieure à celle de la peau non traitée mais irradiée, à toutes les heures de mesure. Cependant, les résultats de la DRS ont démontré que l'écran solaire 5-AO fonctionnait de manière comparable ou mieux que tous les écrans solaires testés avec une dyschromie, un érythème retardé et une pigmentation relativement plus faible.

**Conclusion:** ces résultats mettent en évidence le potentiel des écrans solaires enrichis en AO comme facteur de photoprotection contre LV+UVA1. La combinaison de l'efficacité et de l'aspect esthétique de ce produit peut permettre une plus grande acceptabilité, ce qui est essentiel compte tenu de la disponibilité limitée des moyens de protection contre cette gamme d'ondes.

## INTRODUCTION

Solar radiation from visible light (VL, 400–700 nm) incites skin damage associated with persistent hyperpigmentation, erythema, extracellular-matrix degrading enzymes and free-radical formation [1–9]. Additionally, synergistic effects of VL and long wavelength UVA1 (VL + UVA1, 370–700 nm) have been demonstrated on pigmentation and erythema in melanocompetent (Fitzpatrick skin types IV–VI), and erythema in light skin (Fitzpatrick skin types I–III) individuals [1, 3, 6, 10]. These results have generated interest and research on the photobiology of VL + UVA1, and on photoprotection against their associated cutaneous effects.

Pigmentary changes caused by VL + UVA1 have been shown to occur in three phases: immediate pigment darkening (IPD) which is dose dependent and lasts up to 2 h after irradiation, followed by persistent pigment darkening (PPD) that continues up to 24 h, and lastly delayed tanning (DT) which occurs approximately 5–7 days after irradiation and may last from weeks to months. Both IPD and PPD are suggested to be caused by oxidation and redistribution of pre-existing melanin, whereas delayed tanning is exhibited by the formation of new melanin [11, 12].

Despite VL + UVA1 being associated with pigment darkening and worsening of conditions such as post-inflammatory hyperpigmentation and melasma, there are limited photoprotective options available against this waveband. Currently available organic (chemical) filters do not offer any protection, but tinted sunscreens containing iron oxide or pigmentary titanium dioxide do [13–17]. The fern *Polypodium leucotomos* extract has been shown to down-regulate VL induced pigment darkening when used as an oral supplement and may contribute to protection against VL + UVA1 [18]. Additionally, a recent clinical study showed efficacy of an antioxidant (AO) blend, containing diethylhexyl syringylidene malonate, vitamin C and vitamin E, in offering protection against VL + UVA1 induced erythema in light skinned individuals and pigmentation in dark skinned individuals [19]. With VL + UVA1 induced

**TABLE 1** Products tested

| Products | Description | Sunscreen formula actives/concentration | AO blend/concentration |
|---|---|---|---|
| U | Untreated Irradiated Control | No sunscreen | No antioxidants |
| A | Sunscreen Base SPF 50 no AO | Avobenzone 3%; Octocrylene 10%; Homosalate 10%; Octisalate 5% | No antioxidants |
| B | Sunscreen Base SPF 50 + 3 AO blend | Avobenzone 3%; Octocrylene 10%; Homosalate 10%; Octisalate 5% | Diethylhexyl syringylidene malonate 1%, Vitamin E 0.25% and Ascorbyl Palmitate 0.01% |
| C | Sunscreen Base SPF 50 + 5 AO blend | Avobenzone 3%; Octocrylene 10%; Homosalate 10%; Octisalate 5% | Diethylhexyl syringylidene malonate 0.5%, Vitamin E 0.25%, Vitamin C 0.01%, Licochalcone A 0.025%, Glycyrrhetinic acid 0.01% |
| D | Commercial Tinted Sunscreen SPF 20 | TiO2 10.66% + iron oxides | Tocopheryl acetate |

**TABLE 2** Description of Investigator's Global Assessment scores for pigmentation

| IGA score | Description |
|---|---|
| 0 | None |
| 2 | Mild darkening of the skin |
| 4 | Moderate darkening of the skin |
| 6 | Marked darkening of the skin |
| 8 | Severe darkening of the skin |

effects primarily being mediated by reactive oxygen species (ROS), these findings support the hypothesis that AOs may have a role in mitigating VL + UVA1 effects and should be incorporated in photoprotection [9, 19]. The efficacy of sunscreen products fully formulated with AOs as ingredients, however, needs to be determined. This study evaluated the efficacy of two AO-enriched sunscreen products against VL + UVA1 induced effects. Efficacy was compared with that offered by a commercially available tinted sunscreen product.

## MATERIALS AND METHODS

Ten (10) subjects with SPT IV-VI were enrolled and nine (9) completed the study (9 females; 3 with SPT IV, 3 with SPT V and 3 with SPT VI). The study was approved by Allendale Investigational Review Board and conducted at Dermico Laboratory Broomall, Pennsylvania. Written 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. Those with healthy skin, age 18 or older, with sufficient area on the back with even skin tone and no interfering conditions/marks were included. Subjects that had a current skin condition on their back (e.g. psoriasis, eczema, atopic dermatitis, etc., or active cancer) that the investigator or designee deemed inappropriate for participation or interfered with the outcome of the study, currently taking any anti-inflammatory drugs (e.g. aspirin, ibuprofen, Celebrex [COX-2 inhibitor], corticosteroids), immunosuppressive drugs, or antihistamine medications or had a history of a confirmed or suspected COVID-19 infection within 30 days prior to the study visit or had contact with a COVID-19-infected individual within 14 days prior to the study visit were excluded from the study.

The VL + UVA1 phototesting was performed utilizing the protocol published previously [6, 10, 19]. Briefly, a single VL + UVA1 dose of 380 J/cm$^2$ was administered with a modified solar simulator: Solar Light LS1000 (Solar Light Company Inc, Glenside, PA), with xenon arc lamp and customized filters. Filtered spectral output consisted of 1.4% UVA1 (340–400 nm), 96.3% VL (400–700 nm) and 2.28% IR (700–1800 nm). Spectroradiometric assessment of the long UVA/Visible Light sources was performed with a calibrated spectroradiometer OL-754 (Gooch and Housego, Orlando, FL).

Sunscreen products used include SPF 50 chemical sunscreen without antioxidant blend (A); SPF 50 chemical sunscreen with a three-ingredient AO blend (B); SPF 50 with five-ingredient AO blend (C); and an SPF 20 commercial tinted sunscreen (D). Untreated irradiated control (U) did not have any sunscreen. Information regarding products, including sunscreen active ingredients and AO blends used in the study, are included in Table 1.

On visit 1 (Day 0), 24 h prior to VL + UVA1 exposure, one hundred (100) microliters of products A, B and C were applied on a standard 19 mm Hill Top Chamber System® occlusive patch with a pad (Cliantha Research, St. Petersburg, FL) and placed to the back of subjects on

the marked individual sites for approximately 24 h. These sites, corresponding to organic sunscreen with AO (and without AO to serve as control for impact of occlusion), were occluded to facilitate AO penetration by simulating continuous product use. During visit 2 (Day 1 approximately 24 h after visit 1), the patches were removed and products A, B and C were reapplied at the same occluded sites at a concentration of 2 mg/cm$^2$. One additional site was treated with product D at 2 mg/cm$^2$. The products were allowed to dry for 20 min following which all treated sites A, B, C and D and an untreated site U were irradiated with a VL + UVA1 dose of 380 J/cm$^2$ at an irradiance of 95 mW/cm$^2$ (~1 h and 6 min). Both sites U and A served as positive controls: U because it was untreated but irradiated, and site A because, although treated and irradiated, there was no protection offered by this product against VL + UVA1. Additionally, product A followed the same occlusion process as that for products B and C, further serving as controls for any impact of occlusion.

Assessments of irradiated areas on the back were done by digital cross-polarized photography, investigators global assessment (IGA) score for pigmentation (performed directly on the responses at the subject's back), and diffuse reflectance spectroscopy (DRS). All assessments were performed for all sites immediately (visit 2, Day 1), 24 h (visit 3, Day 2) and 7 days (visit 4, Day 8) after VL + UVA1 exposure. Table 2 includes the pigmentation scale used in this study. For DRS, the instrument consisted of a quartz halogen light source (Ocean Optics, Boca Raton, FL), a bifurcated fibre bundle (Multimode Fiber Optics, East Hanover, NJ), a BWTEK Glacier spectrometer (B&W Tek, Plainsboro, NJ), and a laptop. One leg of the fibre bundle was connected to the light source and the other to the spectrometer. Measurements were performed by placing the common end of the fibre bundle gently against the skin without perturbing blood flow. A reflectance spectrum was acquired in the range of 400–820 nm. Five (5) measurements were collected from each site at all time points after VL + UVA1 exposure. Measurements from normal untreated and non-irradiated skin were also collected for normalization [6, 10, 19]. Apparent concentrations of haemoglobin and melanin, and area under the curve from 400–700 nm (AUC, relative dyschromia) were calculated from the DRS data as described elsewhere [20–22].

Primary data analysis was to compare the pigmentation scores as well as DRS results between control site U (untreated but irradiated) and each of the 3 treated sites B, C and D using paired *t*-tests with the Hochberg multiple comparison methodology. For the 3 comparison results, the smallest *p*-value would be significant if it was less than 0.017, the middle *p*-value if less than 0.033, and the largest *p*-value if less than 0.05. In case

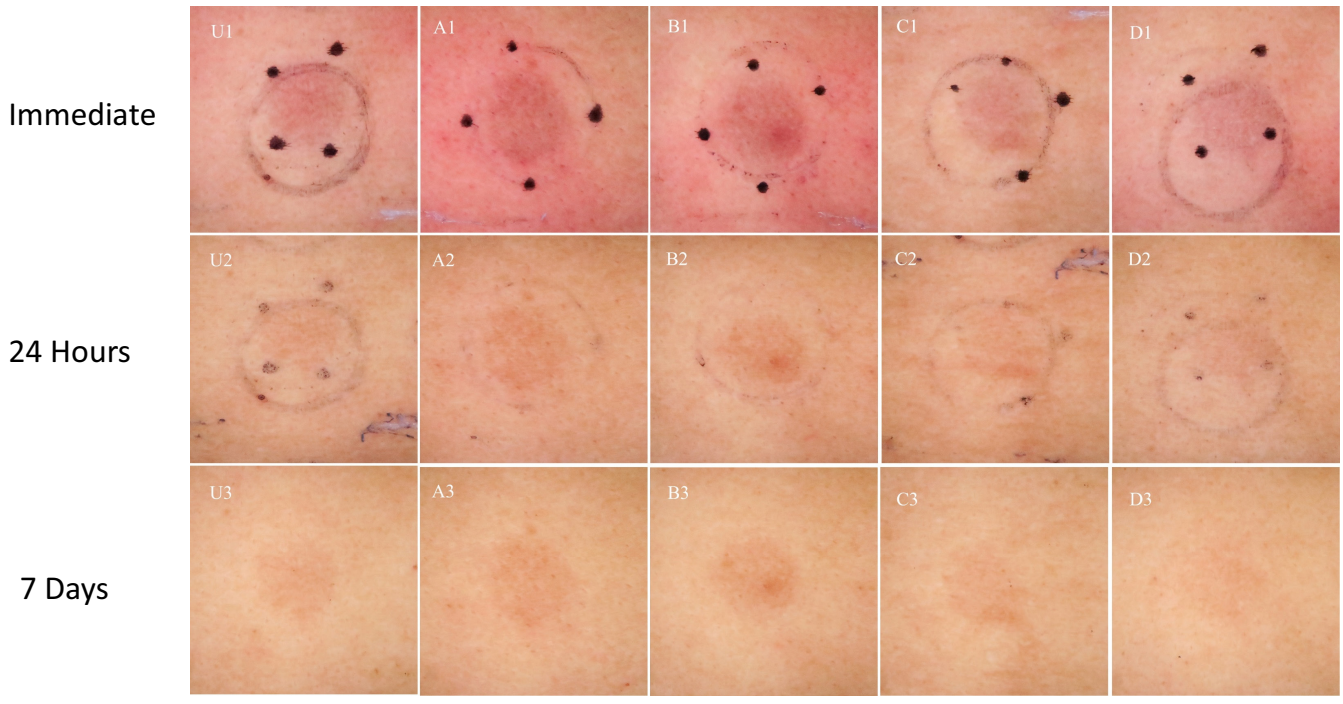


**FIGURE 1** Representative cross-polarized photographs of sites U (untreated irradiated control); (A) (chemical sunscreen filters SPF 50 without antioxidant blend); (B) (chemical sunscreen filters SPF 50 with 3AO blend); (C) (chemical sunscreen filters SPF 50 with 5 AO blend); and (D) (Commercial Tinted Sunscreen SPF 20) of a subject's back at various time points after irradiation (row 1: Immediately after, row 2: 24 h and row 3: 7 days after VL + UVA1 irradiation) [Colour figure can be viewed at wileyonlinelibrary.com]

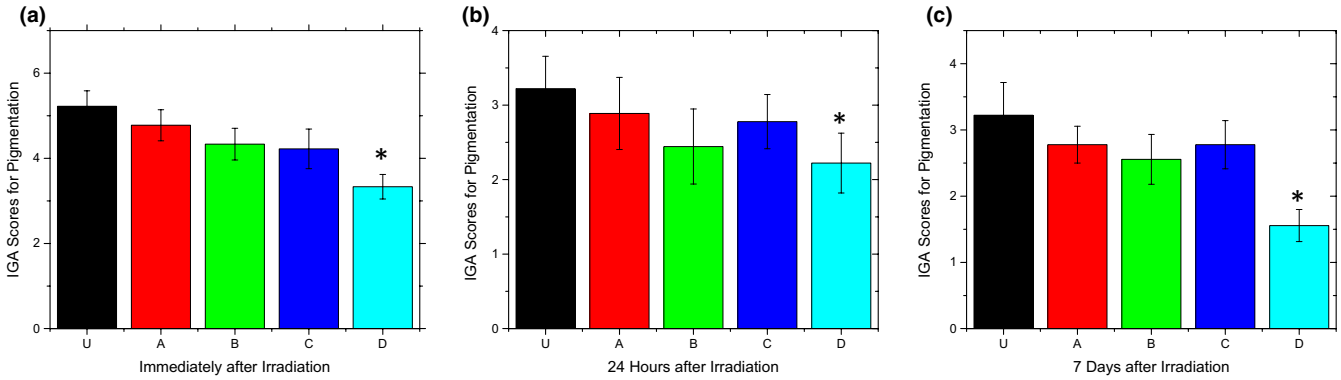


**FIGURE 2** Average IGA scores for pigmentation for all sites immediately (a), 24 h (b) and 7 days after VL + UVA1 irradiation (c). *represents statistically significant difference compared to site U. abbreviations: IGA, Investigator's Global Assessment; UVA1, ultraviolet A1; VL, visible light. U (untreated irradiated control); A (chemical sunscreen filters SPF 50 without antioxidant blend); B (chemical sunscreen filters SPF 50 with 3AO blend); C (chemical sunscreen filters SPF 50 with 5 AO blend); and D (Commercial Tinted Sunscreen SPF 20) [Colour figure can be viewed at wileyonlinelibrary.com]

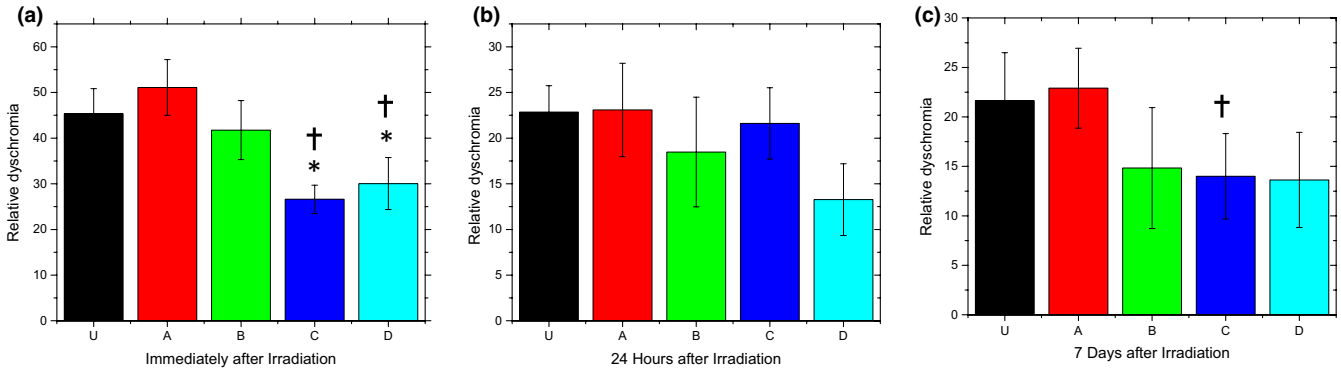


**FIGURE 3** DRS measured relative dyschromia/AUC for all sites immediately (a), 24 h (b) and 7 days after VL + UVA1 irradiation (c). * represents statistically significant difference compared to site U, † represents statistically significant difference compared to site A. Abbreviations: DRS, diffuse reflectance spectroscopy; AUC, area under the curve; UVA1, ultraviolet A1; VL, visible light. U (untreated irradiated control); A (chemical sunscreen filters SPF 50 without antioxidant blend); B (chemical sunscreen filters SPF 50 with 3AO blend); C (chemical sunscreen filters SPF 50 with 5 AO blend); and D (Commercial Tinted Sunscreen SPF 20) [Colour figure can be viewed at wileyonlinelibrary.com]

the t-test assumption of data distribution normality was violated, the Wilcoxon signed rank test was performed instead. As a secondary analysis, similar comparisons were made between control site A (occluded with sunscreen without AO and irradiated) and each of the 3 treated sites B, C and D. Comparisons for pigmentation scores, DRS measured AUC and oxy-haemoglobin were made for each time point, while those for melanin were performed for Day 7 only. All analyses were done using OriginPro software (OriginLab Corporation, Northampton, MA).

## RESULTS

Figure 1 consists of representative cross-polarized photographs of control and treated sites (U, A, B, C and D) of a subject's back at various time points after irradiation (row 1: immediately after, row 2: 24 h and row 3: 7 days after irradiation). Both IPD and erythema were observed immediately after irradiation with relatively less central and surrounding clinical erythema observed for 5AO blend sunscreen (sites C1) and tinted sunscreen (D1) (Figure 1 row 1). As represented in clinical photos obtained 7 days after VL + UVA1 irradiation (Figure 1 row 3), both sites C3 and D3 had relatively less delayed tanning compared with untreated site U3 and that treated with sunscreen without AO, site A3. The average IGA scores for pigmentation as shown in Figure 2 a–c show that the site treated with tinted sunscreen product (product D) was statistically significantly lighter than untreated irradiated control U at all time points. Objective DRS measurements are represented in Figures 3–5 showing changes in AUC/relative dyschromia, oxy-Hb and melanin content, respectively. Figure 3

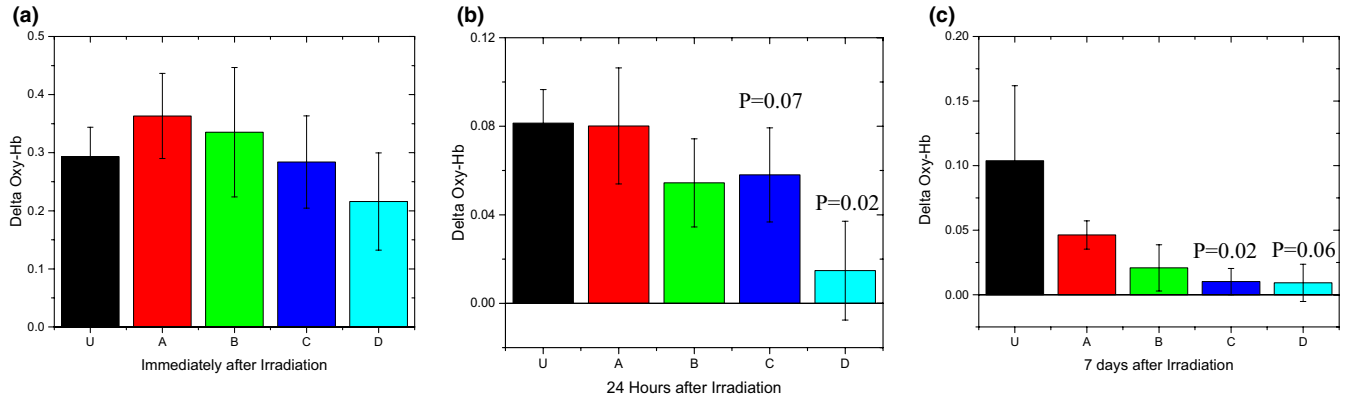


**FIGURE 4** DRS measured change in oxy-Haemoglobin (delta oxy-Hb) for all sites immediately (a), 24 h (b) and 7 days (c) after VL + UVA1 irradiation. Abbreviations: DRS, diffuse reflectance spectroscopy; Hb, haemoglobin; UVA1, ultraviolet A1; VL, visible light. U (untreated irradiated control); A (chemical sunscreen filters SPF 50 without antioxidant blend); B (chemical sunscreen filters SPF 50 with 3AO blend); C (chemical sunscreen filters SPF 50 with 5 AO blend); and D (Commercial Tinted Sunscreen SPF 20) [Colour figure can be viewed at wileyonlinelibrary.com]

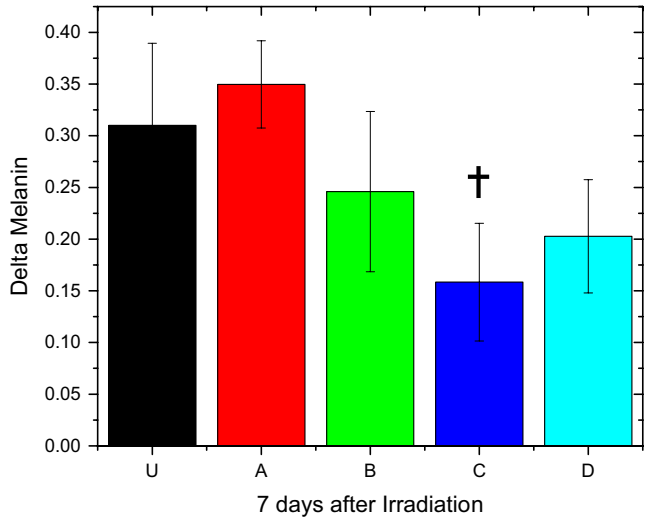


**FIGURE 5** DRS measured change in melanin content (delta melanin) for all sites 7 days after VL + UVA1 irradiation. † represents statistically significant difference compared with site A. Abbreviations: DRS, diffuse reflectance spectroscopy; UVA1, ultraviolet A1; VL, visible light. U (untreated irradiated control); A (chemical sunscreen filters SPF 50 without antioxidant blend); B (chemical sunscreen filters SPF 50 with 3AO blend); C (chemical sunscreen filters SPF 50 with 5 AO blend); and D (Commercial Tinted Sunscreen SPF 20) [Colour figure can be viewed at wileyonlinelibrary.com]

further supports the clinical findings and demonstrates statistically significantly lower relative dyschromia for both 5AO blend sunscreen (sites C) and tinted sunscreen (D) compared with U and A at immediately after irradiation time point (Figure 3a), and for site C compared with site A at 7 days after irradiation time point (Figure 3c). Considering that relative dyschromia/AUC accounts for overall lesion darkness resulting from combination of pigmentation and erythema, separate comparisons for erythema (delta oxy-Hb content) and pigmentation (delta melanin) were also performed. As shown with change in oxy-Hb content in Figure 4a–c, there was less erythema at sites C and D which was markedly below that of site U and was approaching significance at 24 h and 7 days after irradiation time points. Figure 5 represents the same trend for protection by showing change in melanin content 7 days after VL + UVA1 irradiation with site C having statistically significantly lower melanin content compared to site A. Figure 6 compares the absorption spectra of Products C and D; the spectral output of the VL + UVA1 irradiation source is also included demonstrating no impact of SPF on VL + UVA1 protection offered.

## DISCUSSION

VL + UVA1 irradiation has been linked to hyperpigmentation, an observation that is more common in individuals with dark skin phenotypes [6]. Tinted products containing pigmentary titanium dioxide and iron oxides have demonstrated reliable efficacy in decreasing this hyperpigmentation due to associated absorption spectra extending into the VL waveband [23]. However, there are challenges with wider acceptance of these tinted products due to issues with the product colour unfavourably altering skin tone appearance and concerns for sunscreen noncompliance in many skin types [17]. This makes development and efficacy evaluation of other means of photoprotection against the VL waveband necessary.

This study demonstrated the photoprotective efficacy of the 5AO blend sunscreen product against VL + UVA1 induced erythema and pigmentation. The results show that based on clinical scoring, the site treated with tinted sunscreen (Product D) had significantly lower

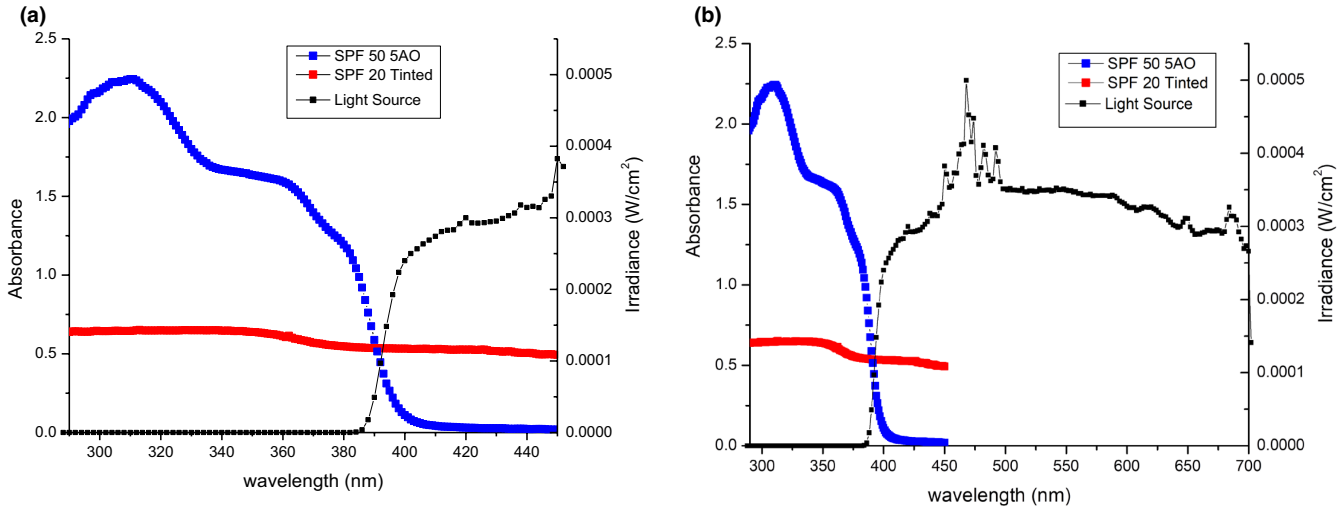


**FIGURE 6** Comparison of absorption spectra of products C and D and the spectral output of the VL + UVA1 irradiation source up to 450 nm (a) Complete spectral output of VL + UVA1 irradiation source along with data presented in 6a (b) [Colour figure can be viewed at wileyonlinelibrary.com]

pigmentation compared with untreated but irradiated skin at all time points after irradiation (Figure 2). However, objective DRS analysis of relative dyschromia (Figure 3) demonstrated that the 5AO blend sunscreen (Product C) performed comparably (Figures 3 and 4), and at times superior (Figure 5), to the tinted sunscreen (Product D) against VL + UVA1 induced effects. The differences, in clinical and instrumental findings, can be explained by the inherent nature of the assessment techniques with clinical scoring being subjective and discrete and DRS being objective and continuous. The continuous nature makes DRS relatively more sensitive in detecting changes in skin colour and chromophore concentrations. As such, the findings indicate that the 5AO blend sunscreen offered photoprotection against VL + UVA1 induced effects without the tint which may lead to wider acceptability among consumers.

The 3AO blend sunscreen (Product B) also demonstrated some photoprotective efficacy (Figures 3–5) against VL + UVA1; however, unlike the 5AO blend sunscreen (Product C), did not reach significance. The enhanced efficacy of the 5AO sunscreen could be associated with the properties of the AOs that were not included as ingredients in the 3AO blend, primarily licochalcone A, glycyrrhetinic acid and vitamin C. Licochalcone A, derived from the roots of *Glycyrrhiza inflata,* has been reported to have antioxidant properties through the inhibition of ROS production in human fibroblasts irradiated by VL in both in vivo and in vitro studies [7, 24]. Glycyrrhetinic acid is a licorice-based compound known to have anti-inflammatory effects against photoaging induced by UV irradiation, contain antioxidant properties, and improve repair of UV-induced pyrimidine dimers [25–27]. The lower concentration of glycyrrhetinic acid and licochalcone A in the 5AO blend sunscreen, 0.01% and 0.025%, respectively, and combined effect with other ingredients may have resulted in the decrease in hyperpigmentation effect observed in our study. Topical solutions of vitamin C, or L-ascorbic acid, have demonstrated antioxidant activity in skin and photoprotective action against UV radiation [28, 29]. Vitamin C's efficacy in reducing UV-induced pigmentation in Fitzpatrick type III skin has been reported [30]. The results indicate that the combination of these 3 AOs with Diethylhexyl Syringylidene Malonate and Vitamin E provided a strong AO defence in mitigating VL + UVA1 induced pigmentation. Nonetheless, the exact mechanism and associated histologic changes still need to be elucidated.

In conclusion, this study demonstrates photoprotective efficacy of an antioxidant-enriched organic sunscreen against VL + UVA1 effects which was comparable to that offered by a tinted mineral sunscreen. The combination of efficacy and the cosmetic appearance of this product may provide wider acceptability which is crucial considering the limited available means of protection against this waveband. The study limitations include small number of participants, limited skin phototype included, the use of a non-validated IGA scale, unavailability of histologic data, lack of colorimetric assessment performed on subjects and the use of SPF 20 for tinted sunscreen product versus the SPF 50 chemical sunscreen. Since SPF pertains to UVB protection, it is not anticipated to have caused variation in the protection offered against VL + UVA1. However, this can be further evaluated in future studies. Future studies may also consider consecutive pre-treatment of AO-enriched sunscreens to ensure proper penetrance and mimic how this product may be used by the typical consumer. Additionally, studies investigating the histologic changes and associated mechanism for 5AO sunscreen

formulation in dark skinned individuals and efficacy in light-skinned individuals are also warranted.

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## CONFLICT OF INTEREST

Indermeet Kohli has served as an investigator/co-investigator for Ferndale, Estee Lauder, La Roche Posay, Unigen, Johnson and Johnson, Allergan and Beiersdorf (previously known as Bayer). IK has received grant support from American Skin Association for a vitiligo project and salary support with Research Career Development award from Dermatology Foundation. IK has served as a consultant for Pfizer, Johnson and Johnson, Beiersdorf and ISDIN. Henry W. Lim has served as investigator/co-investigator for research studies sponsored by Incyte, L'Oréal, Pfizer and PCORI; he has served as a consultant for Pierre Fabre, ISDIN, Ferndale, Galderma, La Roche-Posay and Beiersdorf; he has been a speaker on general education sessions for La Roche-Posay and Cantabria Labs. Iltefat Hamzavi has served as an advisory board member for AbbVie; a consultant for Incyte, Pfizer, Beiersdorf and UCB; a principal investigator for AbbVie, Allergan, Bayer, Clinuvel Pharmaceuticals, Estee Lauder, Ferndale Laboratories, Galderma Laboratories LP, GE Healthcare, Incyte, Janssen, Janssen Biotech, Johnson & Johnson, Lenicura, LEO Pharma, Pfizer, La Roche-Possay, Avita Medical, The Immune Tolerance Network and Unigen with funds paid to the institution; a subinvestigator for Amgen, Bristol-Myers Squibb, Foamix Pharmaceuticals, Pfizer, Incyte and Janssen with funds paid to the institution and co-chair of the Global Vitiligo Foundation. Eduardo Ruvolo is employed by Beiersdorf, Inc. Wyatt Boothby-Shoemaker and Nishant Kumar have no relevant disclosures.

## ORCID

*Wyatt Boothby-Shoemaker* https://orcid.org/0000-0002-2401-0794
*Iltefat H. Hamzavi* https://orcid.org/0000-0002-3137-5601
*Henry W. Lim* https://orcid.org/0000-0002-1576-1115
*Indermeet Kohli* https://orcid.org/0000-0002-2316-6375

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