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Impact of Iron-Oxide Containing Formulations Against Visible Light-Induced Skin Pigmentation in Skin of Color Individuals

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ABSTRACT

Visible light (400–700nm), which contributes to 45% of solar radiation, contributes to skin darkening and worsening of dyschromias, particularly in individuals with Fitzpatrick skin phototypes III and higher. Currently, sunscreens provide limited protection against that spectrum. Due to their capabilities in absorbing, scattering, and reflecting visible light, topical products containing pigments and/or metal oxides can provide additional photoprotection. In this study, the efficacy of two formulations containing iron oxide was evaluated in preventing visible light-induced pigmentation compared with a non-tinted mineral SPF 50+ sunscreen. Expert grading and colorimetry demonstrated that the iron-oxide containing formulations significantly protected against visible light-induced pigmentation compared to untreated skin or mineral SPF 50+ sunscreen in Fitzpatrick IV individuals. These results highlight that iron-oxide containing formulas in a foundation format have dual functions and can provide additional benefits in patients' daily routine by masking existing pigmentation and preventing the development of pigmentation triggered by sunlight exposure, extending protection beyond UV spectrum.

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INTRODUCTION

At the earth's surface, solar radiation comprises of 5–7% ultraviolet (UV), 45% visible light (VIS), and 48–50% infrared (IR) radiation.[1] Studies on the cutaneous impact of radiation have focused on UVB and UVA-mediated effects on the skin. Through different mechanisms, both UVA and UVB are shown to contribute to erythema, tanning, photoaging, and skin cancers.[2]

In recent years, VIS (400–700nm) was demonstrated to induce both immediate and persistent pigment darkening in subjects with skin phototype III and above.[3-5] It has been shown that long wavelength UVA1 (LUVA1) combined with VIS can result in erythema in skin phototype I–III, plus darker, persistent pigmentation and inflammation in subjects with skin phototype IV–VI.[6-8] Various protocols consisting of single or multiple exposures have been published to investigate the mechanism of VIS-induced skin darkening.[3-9] Growing evidence indicates that pigment formed at earlier time points after VIS irradiation is photo-oxidized melanin while, at later time points, new pigments are synthesized through neo-melanogenesis.[5] The proposed molecular mechanism for VIS-induced skin pigmentation is through the activation of Opsin 3, a photo-receptor, which mediates the expression and activity of the rate-limiting enzyme, tyrosinase, in melanocytes.[10,11]

Despite our growing understanding of the impact of VIS on human skin, commercially available sunscreens have a limited ability to extend protection beyond UV. Using a mini-zone back human model, Duteil el al. showed three products containing iron oxide (FeO), titanium dioxide (TiO2), and pigment, provided protection against VIS (400–700nm)-induced pigmentation following 24 hours after a series of four exposures each at a dose of 144 J/cm^2.[9] Another study has shown that topical application of a silicone in water emulsion containing 4.5% yellow FeO reduced VIS-induced pigmentation when compared to unprotected skin after 4 consecutive exposures of 150 J/cm^2.[12] Under real life conditions, daily application of a tinted sunscreen was demonstrated to reduce the appearance of cutaneous hyperchromias after 60 days.[13] Additionally, broad-spectrum sunscreens containing FeO alone or in combination with TiO2 and ZnO were shown to improve melasma lesions after 8 weeks, and to prevent relapses after 6 months.[14,15]

Due to their capabilities in absorbing, scattering, and reflecting visible light, topical products containing metal oxides can provide additional protection.[16] Using a similar exposure protocol as Duteil el al., we evaluated the efficacy of two tinted formulations containing a combination of FeO and TiO2 in comparison to a non-tinted mineral SPF 50+ sunscreen with ZnO and TiO2 for protection against visible light-induced pigmentation. The

mineral SPF 50+ sunscreen was included in the study to assess the efficacy of a UVA and UVB protection alone in blocking the mediated effects of visible light on the skin.

METHODS

Study Participants

The study was performed in accordance with Good Clinical Practices and the principles of the Declaration of Helsinki. The procedures used in this study were approved by IntegReview IRB (Austin, TX). Before any study procedure, the subjects received the necessary written and verbal information and signed an informed consent form. Eligibility was determined by physical examination and confirmation of all inclusion/exclusion criteria. Ten healthy women aged 18-50 years (mean age, 35 + 6 years) with Fitzpatrick skin phototype IV were included in this study. Subjects with planned UV exposure (sunlight or sunbeds) or who used laser or phototherapy to the back during the study; with a history of taking or planned on taking any photosensitizing, anti-inflammatory, immunosuppressive medications, or any medication known to cause abnormal responses to UV exposure; or having prior or current pathologies induced or aggravated by exposure to light, or having abnormal reactions to sunlight (eg, photosensitive dermatitis, skin cancers, solar urticaria), were excluded.

Study Design

The study was monocentric, randomized, and single-blinded. Following the screening visit, subjects were required to attend six evaluation visits as follows:

At baseline (day 0), five investigational zones of 2x2 cm were delineated on the middle section of each subject's back: one negative control zone (unexposed and un-irradiated), one positive control zone (only irradiated), and three pre-treated and irradiated zones. The three test products were applied (2 mg/cm^2) according to randomization plan.

On day 0, fifteen minutes after product application, the four test zones, excluding the negative control zone, were exposed to a single dose of VIS at 144 J/cm^2, equivalent to one hour of exposure at midday in summertime. Product application and VIS exposure were similarly repeated on day 1, day 2, and day 3.
Clinical grading for skin pigmentation, colorimetric measurements, and standardized photograph were performed before product application and VIS irradiation on day 0 to day 3, 24 hours post the last irradiation on day 4, and on day 14.

Test Materials

Test materials consisted of three currently marketed products: 1) Product A (mineral SPF 50+ sunscreen with ZnO and TiO_2); 2) Product B (FeO and TiO_2 formulation); and 3) Product C (FeO formulation). Figure 1A displays the concentrations of the metal oxides in each test products, and Figure 1B, their absorbance spectra within the UV and HEV range. Product B and C have wider absorption wavelength band extending in the HEV range, suggesting superior protection compared to Product A. All test products were applied in a randomized and single-blinded manner.

Solar Stimulator

An ORIEL solar simulator, model 94043A-SP01-1600W, was used (Stratford, CT, USA). Its artificial luminous source was composed of a 1600 Watts xenon arc lamp, giving a continuous spectrum covering ultraviolet (280nm) to infrared (1720nm). The light source was fitted with an AM 1.5G filter to generate the standard solar spectrum.

The Schott WG 400nm filter was used to eliminate UVR, allowing only VIS and IR spectra to pass through. A Schott KG3/2mm filter was then used to output mostly VIS and some IR-A emission (400–900nm) as illustrated in Figure 1C. The resulting spectral output, which will be referred to as visible light*, contained no UVB, 0.01% UVA (320–400nm), 88.2% VIS (400–750nm), 10.7% HEV (400–450nm), and 9.8% IRA (750–900nm). For each test zone, light intensity was measured just prior to exposure in order to deliver an accurate dose of 144 J/cm^2, with an average fluence rate of 50 mW/cm2.

Pigmentation Assessments

The intensity of the induced skin pigmentation was visually assessed by expert grading using an internally validated scale, ranging 0 (no pigmentation) to 13 (pronounced brown pigmentation). The scale is based on the visual comparison of the pigmentation of the test zone with that of the surrounding unexposed control skin. Scoring was performed by the same clinical expert throughout the study.

The instrumental measurements of skin color were performed before the subject inclusion and during the study, with a Chromameter® (Konica Minolta CR400), using the $L^*a^*b^*$ color system (CIE lab, 1976). The individual typology angle (ITA°) that defines skin fairness or darkness was calculated from L^* and b^* measurements, using the formula: $ITA° = [\text{arcTangent } (L^* - 50)/b^*)]\ 180/\pi$.

Skin color changes after irradiation were assessed by using the parameter $\Delta E = \sqrt{(\Delta L^2 + \Delta a^2 + \Delta b^2)}$, where ΔL is the difference between the L of exposed zone and the non-exposed zone. Similar calculations were performed for Δa and Δb.

Standardized photographs were taken using a Canon EOS Rebel T5 camera with standard cross polarized filters under the same source of artificial light.

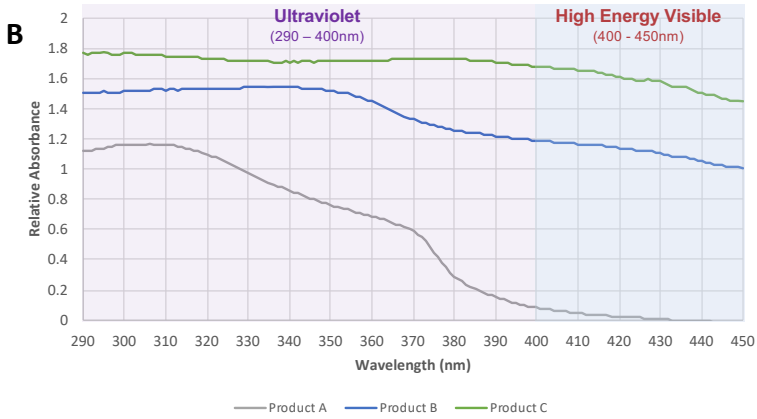
Statistical Analysis

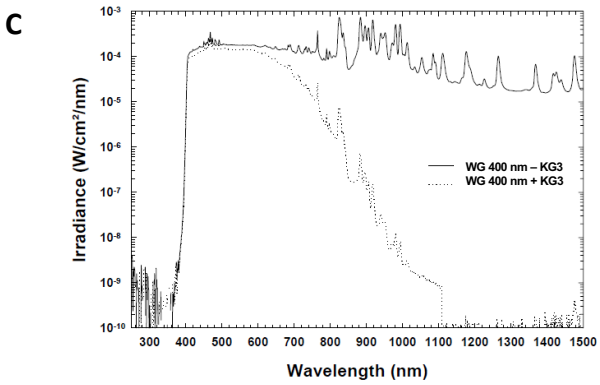
For pigmentation score, L^* value, a^* value, b^* value, ITA°, and Delta E, a Gaussian linear mixed model was used to analyze the mean difference in change from baseline between treatment with baseline, treatment, time, treatment-time interaction as

FIGURE 1. (A) Metal oxide content in the formulas; (B) UV and HEV absorption spectra of tested products; (C) Spectral irradiance of solar simulator between 250–1500nm with WG 400nm + KG3 filters.

A

Products	ZnO	TiO_2	FeO
Product A (mineral SPF50+)	6.5%	4.5%	0%
Product B	0%	27%	4.85%
Product C	0%	0%	27.25%





fixed effects, and subject as random effect. *P*-values <0.05 were considered statistically significant.

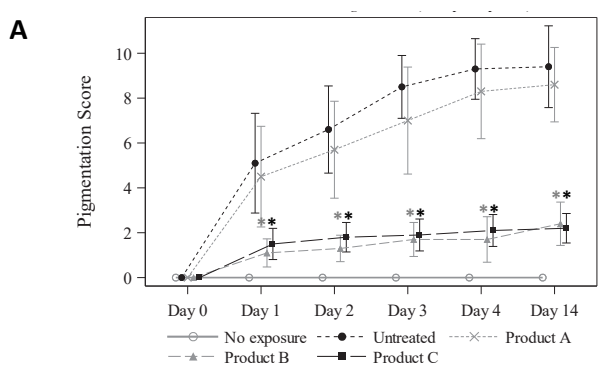
For visible light protection factor (VL-PF), the slope from baseline to day 4 of estimated ITA° change from baseline was calculated, and the ratio between the mean slope for the VL-irritated bare skin over the mean slope of the VL-irritated skin treated with one of the products was obtained as the VL-PF. All calculations were performed using SAS ver 9.0.

RESULTS

Clinical assessment for skin pigmentation, including statistical comparisons to baseline values, for each treatment from day 0 to day 14, are illustrated in Figure 2A. The untreated zone and the zone pre-treated with Product A showed a perceivable and statistically significant increase in pigmentation from day 0 to day 3, which was persistent to up to day 14. Pre-treatment with Products B and C demonstrated a statistically significant but less-pronounced increase in pigmentation, which was maintained at minimal level following the series of four consecutive exposures to visible light* and until day 14, as shown in Figure 2B.

The mean values of ΔL^* are shown in Figure 3A. In alignment with clinical assessment for skin pigmentation, untreated zone and Product A presented a statistically significant decrease in

FIGURE 2. (A) Clinical grading of pigmentation score for the 3 products and comparison to non-exposed control and untreated-VIS exposed control. *denotes *P*<.001 for Product B and C compared to untreated and Product A; (B) Representative images of visible light-induced pigmentation observed at indicated timepoints.



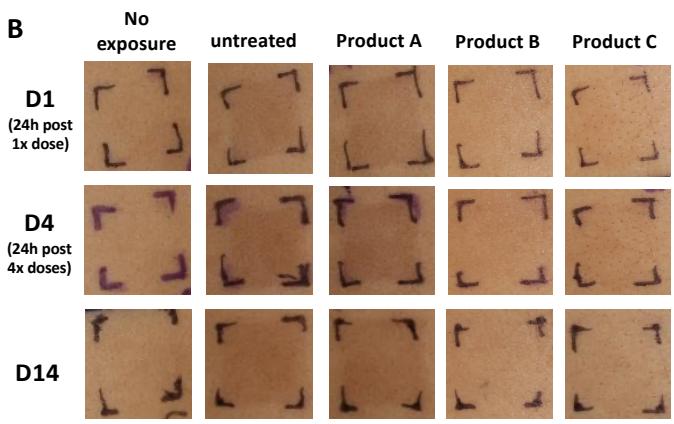


FIGURE 3. Change in efficacy parameters, (A) ΔL*, (B) ΔE, and (C) ΔITA° with comparisons from baseline. *denotes *P*<.001 for Product B and C from untreated and Product A.

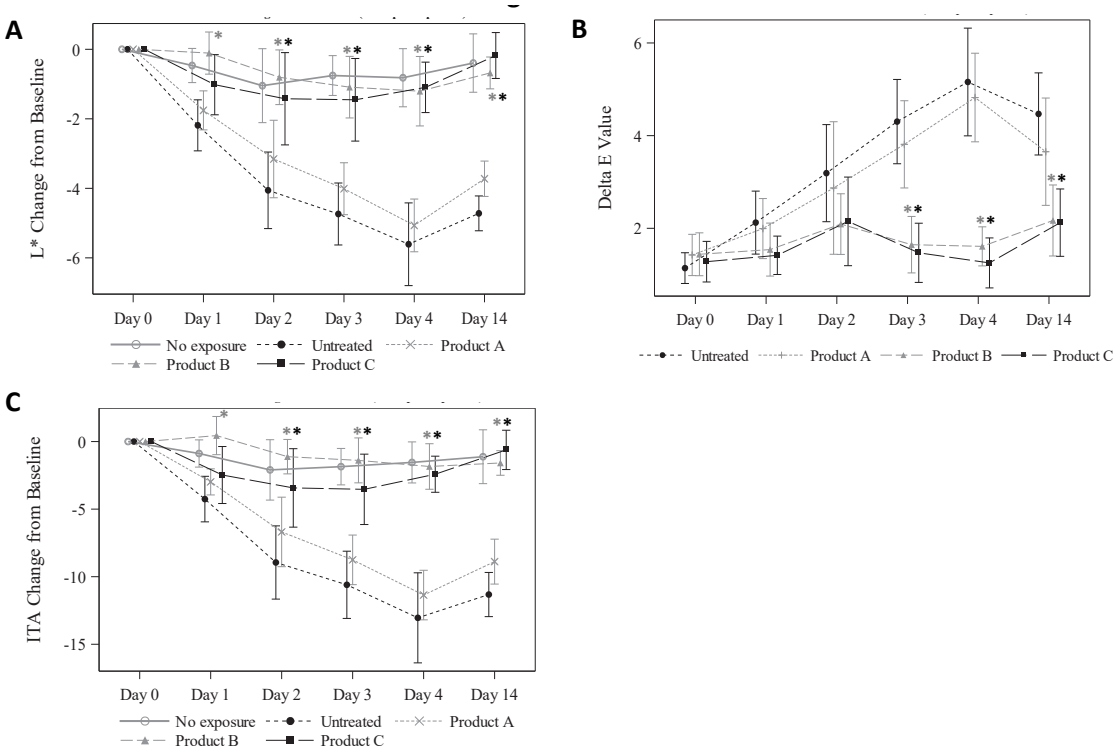


TABLE 1.

Pairwise comparisons between products. Statistical significance, *P*<0.05; trend towards statistical significance, *P*<0.1>0.05; ns, not significant.

Parameters	Comparisons	p values Day 1	p values Day 4	p values Day 14
Clinical Scoring	Untreated vs. Product A	ns	ns	ns
	Untreated vs. Product B	<0.001	<0.001	<0.001
	Untreated vs. Product C	<0.001	<0.001	<0.001
	Product A vs. B	<0.001	<0.001	<0.001
	Product A vs. C	<0.001	<0.001	<0.001
	Product B vs. C	ns	ns	ns
ΔL*	Untreated vs. Product A	ns	ns	0.035
	Untreated vs. Product B	<0.001	<0.001	<0.001
	Untreated vs. Product C	<0.001	<0.001	<0.001
	Product A vs. B	<0.001	<0.001	<0.001
	Product A vs. C	0.072	<0.001	<0.001
	Product B vs. C	0.064	ns	ns
ΔE	Untreated vs. Product A	ns	ns	ns
	Untreated vs. Product B	ns	<0.001	<0.001
	Untreated vs. Product C	ns	<0.001	<0.001
	Product A vs. B	ns	<0.001	0.005
	Product A vs. C	ns	<0.001	0.005
	Product B vs. C	ns	ns	ns
ΔITA°	Untreated vs. Product A	ns	ns	0.041
	Untreated vs. Product B	<0.001	<0.001	<0.001
	Untreated vs. Product C	ns	<0.001	<0.001
	Product A vs. B	<0.001	<0.001	<0.001
	Product A vs. C	ns	<0.001	<0.001
	Product B vs. C	0.015	ns	ns

ΔL* from day 0 to day 14 (indicating skin darkening); whereas, compared to baseline, both Product B and C showed a statistically significant, less-marked decrease in ΔL* at all timepoints except at day 1 and day 14 (indicating less skin darkening).

For clinical grading of pigmentation, pairwise comparisons between various zones presented in Table 1 illustrate no statistical difference between untreated zone and Product A on day 1 (after the 1st exposure), day 4 (24 hours after the last exposure), and day 14. Despite no significant difference between Product B and C, both showed statistically significant differences when compared to untreated zone and Product A at all timepoints.

For ΔL*, there was no statistical difference between untreated zone and Product A at day 1, day 3 (p value not shown), and day 4, and a statistical difference at day 14, favoring Product A. Product B demonstrated significant higher ΔL* compared to exposed zone and Product A at all-time points. Compared to untreated zone, Product C showed significant higher ΔL* at all-time points (less skin darkening), from day 2 (p value not shown) to day 14 when compared to Product A. These results suggest that both Products B and C were equally effective in blocking visible light*-induced skin pigmentation.

Similar results were observed for ΔE and ΔITA° parameters (Figure 3B, 3C, and Table 1). Product A was similar to untreated zone at all timepoints for ΔE, and same for ΔITA°, except at day 14. Both Products B and C were more effective in preventing skin color change compared to Product A from day 2 for ΔITA° and from day 3 for ΔE. No statistical differences in performance between Products B and C for ΔE, and same for ΔITA°, except a statistical difference at day 1, favoring Product B.

Skin redness (Δa*) and skin yellowness (Δb*) showed much smaller changes over time and inconsistent results for product performance distinction, indicating that the blocking of the visible light*-induced pigmentation by the products were specific for skin darkening (data not shown).

DISCUSSION

Originally believed to be harmless, it seems evident that VIS induces biological effects to human skin.[17] Combining LUVA1 and VIS cause an immediate erythema response in skin phototype I-III, while inducing inflammation and immediate pigment darkening in skin phototype IV-VI.[6-8] VIS alone or in combination with IR generates ROS, increases collagen degradation, and indirectly leads to DNA damage.[18,19] Since VIS and IR makeup a great proportion of solar radiation and due to the lack of sunscreens offering protection beyond UV, it is crucial that novel means of photoprotection against these longer wavelengths be developed and tested. Here, we demonstrate that FeO containing formulations were more effective in preventing visible light-induced pigmentation compared to a non-tinted mineral SPF50+ sunscreen.

Similar to UVA, VIS elicits immediate and persistent pigment darkening (PDD) in subjects with skin phototype III and above; processes that are mediated via the photo-oxidation of pre-existing melanin and de-novo melanogenesis, respectively.[4,20-22] The potential topical or oral use of antioxidants, molecules that scavenge free radicals, for VIS protection, has been proposed and tested by various research groups.[23-26] However, clinical studies evaluating the efficacy of antioxidants to protect against VIS-induced pigmentation are scarce. One study demonstrated that topical application of an antioxidant mixture reduced the immediate erythema and pigmentation responses followed by VIS+UVA1 exposure in subjects with skin phototypes I-III and IV-VI, respectively.[27] But, this protective trend was not observed at day 7, indicating that antioxidants may be more effective in reducing skin darkening mediated by melanin photo-oxidation, and less effective at preventing de-novo melanin synthesis, which constitutes the later phases of pigment formation. Our results show that both FeO-containing formulations tested efficiently prevented further skin darkening following each irradiation, which persisted up to 14 days, while the mineral SPF50+ sunscreen gave similar results as untreated skin. Due to their higher concentrations of metal oxides, particularly FeO, it is clear that these formulations provided a better physical barrier for the skin against VIS rays, defending against cumulative effects and inhibiting delayed tanning.

Interestingly, despite the difference in FeO and TiO2 levels (Figure 1A), there lacked statistically significant differences in performance between formulations B and C. This raises an important point concerning how to assess products photoprotective efficacy against VIS, as it is performed for UVB and UVA sunscreens under regulatory guidelines.[28-30] Several papers have suggested different in vivo methods to evaluate the VIS protection factor (VL-PF) of products.[9,12,31,32] For single dose exposure, the VL-PF is based on the minimal PPD of unprotected and protected skin, similar to the UVA protection factor method.[12] More recently, Kholi et al proposed to use the spectral signatures of the VIS+UVA1-induced skin pigmentation by obtaining the ratio of the area under the curve of the differential apparent absorbance of untreated skin from 400–700nm to that of treated skin at specific timepoints.[31] For multiple doses, Duteil et al determined the VL-PF by obtaining the ratio of the mean slope of the linear regression calculated between timepoints of the ΔITA° curves for untreated over treated.[9] Using similar method, the calculated VL-PF of Product A (mineral SPF 50+) was 1.48, while Product B and Product C had a VL-PF of 7.07 and 5.4. In alignment with prior studies, it appears that products with FeO pigments present higher VL-PF, as compared to products without pigment.[32] Despite the big differences in the FeO content between product B and C, in this study, we found both products demonstrated similar VL photoprotection. Future studies are needed to expand on the findings of this pilot study with bigger sample sizes, longer evaluation time beyond 14 days, determination of the minimal level of FeOs necessary for effective VIS

protection, and development of standardized guidelines for in vivo assessments of VL-PF and interpretation of this value.

CONCLUSION

In summary, our results show that products containing FeO protect the skin from VIS-induced pigmentation better than a mineral SPF50+ sunscreen containing TiO2 and ZnO. These findings highlight that FeO pigments-based foundation formulations can play a dual role by camouflaging existing pigmentation, as well as reducing the development of pigmentation triggered by sun exposure. The rising evidence that VIS and IR can induce long lasting biological responses in human skin has created the need to find non-traditional strategies for full spectrum photoprotection and beyond the UV range. Moreover, it is essential to identify different ways to bring clinically visible benefits that are compatible to daily routines of patients for minimizing the damaging effects of chronic sun exposure. The availability of topical products containing pigments and/or metal oxides, such as foundations in multiple shades and tones, can offer customized daily protection beyond UV for individuals of all skin phototypes.

DISCLOSURES

Pearl Grimes serves as a consultant for VT Cosmetics, Incyte and Dermaforce; as an investigator for Aclaris Therapeutics, Allergam, Pfizer, L'Oreal, Johnson & Johnson, Clinuvel, Thync Global Inc., VT Cosmetics and Incyte. All other authors are employees of L'Oreal Research & Innovation, USA.

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