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Efficacy of Ceramide-Containing Formulations on UV-Induced Skin Surface Barrier Alterations

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ABSTRACT

The human skin, particularly the stratum corneum, serves as a protective barrier against exogenous factors, including ultraviolet radiation (UVR) and pathogen invasions. The impact of UVR on skin cancer and photoaging has been extensively studied. However, the direct impact of UVR on skin barrier integrity under clinical settings remains poorly explored. Due to their benefits in reducing inflammation and promoting skin barrier repair, ceramide-containing formulations can provide added photoprotection benefits. In this study, the efficacy of a ceramide-containing sunscreen and moisturizer were evaluated in preventing UV-induced skin surface barrier changes. Expert grading, instrumental, and tape-stripping assessments demonstrated that UVR induced erythema and hyperpigmentation and caused changes in skin cells surface morphological organization and maturation. Treatment with a ceramide-containing sunscreen and moisturizing cream routine reduced erythema and hyperpigmentation, improved skin hydration, and maintained normal superficial skin cells morphology and turnover after UVR. Our results indicate that barrier-enforcing lipids formulations can provide additional benefits in patient's daily routine by strengthening the barrier and improving skin health overall against chronic sun exposure.

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INTRODUCTION

The epidermis, the skin's outermost layer, functions as a barrier against environmental aggressors through the cornification of keratinocytes to form the stratum corneum (SC). Embedded within a lipid matrix that mainly comprises cholesterol (CHOL), free fatty acids (FFAs), and ceramides (CERs), corneocytes undergo a maturation process that is essential to maintain proper SC barrier integrity and function.[1]

Solar ultraviolet radiation (UVR), comprised of ~95% UVA (320–400 nm) and ~5% UVB (280–320 nm), is a prominent environmental skin stressor.[2] Numerous in vivo and ex vivo models have been developed to evaluate the impact of UVR on skin barrier, revealing mixed results. For instance, UVB and UVA irradiations were shown to increase SC triglycerides, FFAs, alkanes, and squalene levels in subjects with skin phototype II–III.[3] Interestingly, UVB exposure alone decreases SC lipid cohesion and damages intercellular barrier permeability formed by tight-junctions.[4,5] One research group evaluated the impact of UVR on skin biophysical properties on subjects with skin phototype II–IV. They found that UV exposure at various minimal erythema (MED) doses increased trans-epidermal water loss (TEWL) and decreased skin hydration in a dose-dependent manner within 24 hours, suggesting impaired barrier function.[6] Another study demonstrated that 1.5 MED did not affect skin hydration, but increased TEWL after 72 hours. They also observed a decrease in total CERs and increase in CHOL, indicating that alterations in SC lipid content in response to UV may disrupt barrier integrity.[7]

Under real life conditions, chronic sun-exposed hands of middle-aged Japanese golfers were shown to be photodamaged and to have reduced skin hydration, but interestingly, no difference in TEWL compared to the glove-protected hands.[8] It was also demonstrated in Chinese subjects that skin barrier recovery after tape-stripping was not as efficient for body sites exposed to sunlight compared to non-exposed.[9] Overall, these findings indicate that depending on the nature of exposure and skin phototypes, UV-induced changes in skin barrier-related endpoints will greatly vary and may contradict one another. Thus, further studies are needed.

Prior studies have shown that application of an equal ratio of SC lipids promotes barrier repair, and increasing their ratios accelerate recovery.[10] Because of their skin benefits, intercellular lipids, particularly CERs, are now commonly used as prominent ingredients in moisturizers for managing several dermatologic conditions.[11–13] Moreover, many models have been used to evaluate the efficacy of various natural lipid mixtures for optimizing barrier repair in response to exogenous stimuli. For example, Byun et al reported that topical application of CHOL decreased elicited inflammatory response on tape-stripped human skin irradiated with UV while linoleic acid and N-oleoyl-phytosphingosine promoted cell death and inflammation, respectively.[14] Additionally, synthetic CERs are also shown to promote faster barrier recovery after various stimuli, including UV and tape-stripping.[15]

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Despite our growing understanding of the benefits of lipids-containing formulations in promoting skin barrier repair, there is limited knowledge on the clinical efficacy of these formulations following UV exposure. In our study, we investigated the impact of UVR on skin surface barrier properties and evaluated the protective efficacy of a ceramide-containing sunscreen and moisturizing cream.

METHODS

Study Participants

The study was monocentric, randomized, and double-blinded, and 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 (Texas, USA). Before any study procedures, the subjects received the necessary information and provided informed consent. Eligibility was determined by physical examination and confirmation of all inclusion and exclusion criteria. Sixteen healthy men and women aged 18–50 years (mean age, 33 years) with Fitzpatrick skin phototype III and an average individual typology angle (ITA°) of 34.9 completed the study.

Solar Stimulator

An ORIEL solar simulator, model 92292-1000 sn 115, was used (Newport, USA). Its artificial luminous source consisted of a 1500 Watts xenon arc lamp, giving a continuous spectrum covering UV (240 nm) until infrared (>800 nm). It included a dichroic mirror that passes 280–400 nm to greatly reduce visible to infrared output. Schott WG 320/2.6 mm filter was used to obtain UVR spectrum (290–400 nm). For each test zone, light intensity was measured just prior to irradiation with a calibrated PMA 2100 radiometer (Solar Light Co., USA), equipped with dUVA and erythema optimal sensors.

UV Irradiation

UV exposure was performed in two consecutive procedures. First, the MED of individual (MEDi) subjects was determined during screening. Six areas of 2.25 cm^2 on the back of each subject were exposed with UV doses using a 1.25 geometrical progression. The starting UV dose was calculated according to the ITA° mean measured on the six areas. MEDi of each subject, with an average of 0.06 J/cm^2, were evaluated 24 hours after irradiation. Secondly, at baseline (day 0), all test zones, excluding MED sites, were irradiated with a single dose of 2 MED.

Test Materials

Test materials consisted of a currently marketed multilamellar vesicular emulsion ceramide-containing sunscreen SPF 25 (SPF) and moisturizing cream (Moisturizer), which were applied at 4 mg/cm^2.

Study Design

On day 0, five test zones of 16 cm^2 were delineated on the middle section of each subject's back: one negative control (untreated and UV-irradiated), one positive control (UV-irradiated only), and three treated and UV-irradiated. The four irradiated zones, excluding the negative control, were exposed to 2 MED. According to a randomization plan, out of the three treated and UV irradiated zones, one received the SPF 15 minutes before exposure on day 0; another received the Moisturizer immediately after exposure on day 0, plus once a day for another nine days (day 1 to day 4 and day 7 to day 11); and the third zone received both the SPF and Moisturizer, as respectively described.

All evaluations were conducted in a room under controlled temperature (22 °C) and relative humidity (40%) after subjects acclimated for at least 15 minutes. Clinical grading for skin pigmentation and erythema, plus standardized photographs were performed at baseline (before product application and UV exposure), day 1, day 7, and day 14; TEWL and skin hydration measurements from day 1 to day 4, day 7 to day 11, and on day 14; and tape-stripping at baseline, day 1, and day 14.

Pigmentation and Erythema Assessments

Skin pigmentation and erythema were visually assessed by expert grading using an internally validated scale, ranging 0 (absence) to 13 (pronounced brown or pink). The scale is based on the visual comparison of the skin color of the test zone with that of the surrounding unexposed control skin. Scoring was performed by the same clinical expert throughout the study. Standardized photographs were taken using a Canon EOS Rebel T5 camera with standard cross polarized filters under the same source of artificial light.

Transepidermal Water Loss (TEWL) and Skin Hydration Measurements

TEWL was assessed to evaluate skin barrier function using a Tewameter (Model TM300; Courage-Khazaka, Germany). Results were expressed in grams of water per unit area of skin per unit of time ($g/m^2/h$), as mean values of the measurement performed on three different areas within the test zone. Skin hydration was assessed using a Corneometer (Model CM825; Courage-Khazaka, Germany). Results were expressed in arbitrary units, as mean values of the measurement performed on five different areas within the test zone.

Tape-stripping Procedure

Tape stripping was performed using 22 mm D-Squame disc (CuDerm Corporation, USA). Six consecutive tapes were placed onto cleaned test sites with even pressure using a pressure plunger before being slowly removed with forceps. The first two tapes were disregarded and the four subsequent tapes from the same location were collected and stored at -80 °C. Tape strips from six subjects out of sixteen who completed the study and whom we considered best responders based on clinical

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assessments were chosen for further analysis.

Corneocyte Cornified Envelope (CE) Maturation

Corneocyte CE maturation technique is based on the double-staining of CE-bound lipids with Nile red and CE structural protein with involucrin. CE maturation was evaluated from the fourth D-Squame of the six mentioned subjects. Briefly, half of the tapes were extracted following Sylnevia laboratory (Labège, France) isolation protocol. Isolated CEs in suspension were placed onto microscope slides and incubated with involucrin primary and respective secondary antibodies before being washed and mounted with Nile red. Images of both Nile red-stained and involucrin immunostained corneocytes were taken separately with a fluorescence microscope (ZEISS, ApoTome). IMAGEJ image analysis software was used to analyze the red pixels obtained from the Nile red stained mature cells and the green pixels from the involucrin immunostained immature cells. The ratio of red /green pixels corresponds to the CE maturation.

Skin Surface Isotropy Assessment by Scanning Electron Microscopy (SEM)

The other half of the fourth D-Squame of the six mentioned subjects were prepared for visualization with SEM (Quanta 250 FEG FEI; ThermoFisher Scientific, USA) by Sylnevia laboratory. Briefly, after being coated with a thin layer of gold, the samples were placed in the microscope, where 36 images per group were taken (6 subjects; 2 timepoints; 3 magnifications: x50, x250, and x500), for a total of 180 images. High-resolution pictures were taken and evaluated in a blinded fashion by one scientist. Adapting the semiquantitative scoring system of Fluhr et al, for SC surface isotropy (ie, micromorphology organizational patterns), three parameters were assessed: cellular clusters at x50, dispersion at x250, and differentiated single cells appearance at x500.[16] Scoring for each parameter according to defined criteria was translated into a quantitative scale from 0 to 3. The sum of individual scores obtained after evaluation of the three parameters gives a skin surface isotropy score. Lower score corresponds to a more disorganized SC surface morphology (low isotropy).

Statistical Analysis

For pigmentation and erythema clinical scores, TEWL and hydration index, linear mixed models were used to analyze longitudinal data with change from baseline as response vector; baseline, time, treatment and treatment-time interaction as fixed effect; and subject as random effect. *P* values were adjusted with Benjamini-Hochberg approach for TEWL and Hydration Index, and a signed-rank Wilcoxon test for pigmentation and erythema scores.

For tape-stripping analysis endpoints, data were analyzed to determine mean, and standard error with normality not assumed according to the number of samples per group. Bonferroni's multiple comparison test was first performed, followed by a Wilcoxon matched-pairs signed rank test to compare each condition at each time points. *P* values <0.05 were considered statistically significant.

RESULTS

Skin Color Change after UVR

Clinical assessment for erythema and skin pigmentation are illustrated in Figure 1A and 1B, respectively. UVR elicited a perceivable and statistically significant increase in erythema, peaking at day 1 and recovering to baseline by day 7. Treatment with SPF or SPF+Moisturizer routine presented with a significantly less-marked increase in erythema; while treatment with Moisturizer showed no significant effect and was similar to UV only (Figure 1A). For skin pigmentation, UV induced a noticeable and statistically significant skin darkening response, which persisted up to day 14. Treatment with SPF or SPF+Moisturizer routine presented a statistically significant, but less-pronounced increase in pigmentation, which was maintained at minimal level following irradiation until day 14; whereas treatment with Moisturizer showed no significant effect (Figure 1B and 1C). Pairwise comparisons reveal no statistical difference between UV only and Moisturizer for erythema and pigmentation. Treatment with SPF or SPF+Moisturizer routine showed similar performance and were most effective in reducing both erythema and hyper-pigmentation after UVR at all timepoints (Table 1).

Skin Barrier Properties (Hydration and TEWL) after UVR

Next, we investigated the impact of UV on skin barrier by assessing skin hydration and TEWL. There was no statistical difference in skin hydration between control and UV only zones (Figure 2A). Compared to UV only, SPF+Moisturizer routine showed an increasing statistical trend in skin hydration at day 1, and demonstrated significant higher hydration levels by day 3, day 7 and day 14. Treatment with Moisturizer alone showed an increasing trend in skin hydration at day 3 and significant improvement by day 14 compared to UV only, while treatment with SPF showed improved skin hydration only at day 14 (Figure 2A and Table 1). These results suggest that SPF+Moisturizer routine and Moisturizer alone, to a lesser extent, were both effective in promoting skin hydration following UVR.

TEWL showed smaller variations over time following UV, inducing no significant change in all conditions (Figure 2B). Table 1 illustrates no statistical differences in performance between treatments, except at day 3, where SPF+Moisturizer routine showed significant reduced TEWL compared to UV only.

Corneocyte Visualization and Maturation after UVR

To further elucidate the impact of UV on skin barrier integrity, we determined whether UVR affects the superficial SC surface

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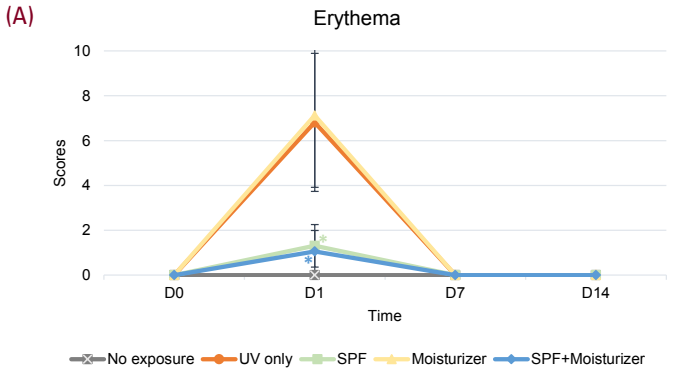
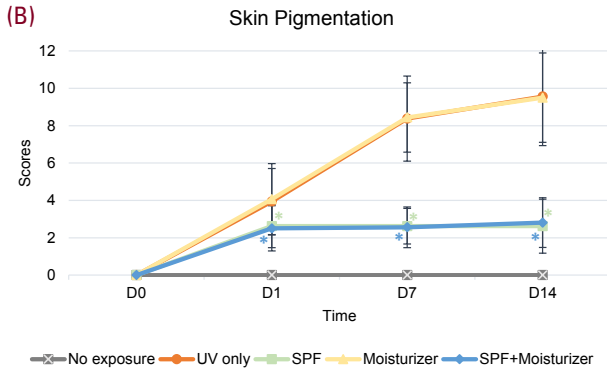
FIGURE 1. Sunscreen alone or in combination with moisturizer decrease UV-induced erythema and hyperpigmentation, while treatment with moisturizer alone was similar to UV only site. (A) Clinical grading of erythema and (B) pigmentation scores for each condition following UV exposure. (C) Representative images of UV-induced erythema and pigmentation responses for each condition at indicated timepoints.





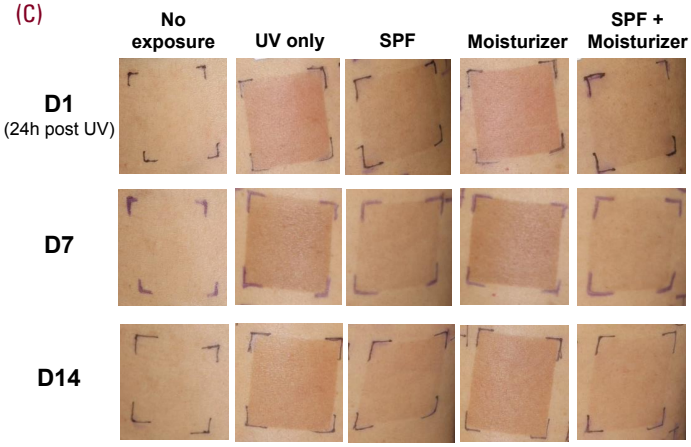


TABLE 1.

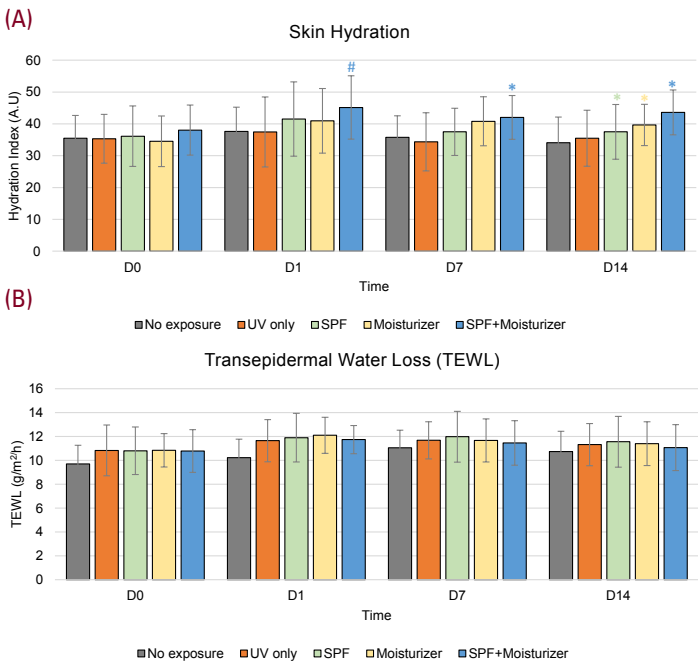
Efficacy of Each Product for Indicated Endpoints and Timepoints

Parameters (Compared to UV only)	SPF				Moisturizer				SPF+Moisturizer			
	D1	D3	D7	D14	D1	D3	D7	D14	D1	D3	D7	D14
Erythema	↓				↔				↓			
Hyperpigmentation	↓		↓	↓	↔	↔	↔	↔	↓		↓	↓
Skin Hydration	↔	↔	↔	↑	↔	↑	↔	↑	↑	↑	↑	↑
Barrier Function Impaired (TEWL)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↓	↔	↔
Irregular Skin Cells Appearance	↔			↓	↔			↓	↓			↓

↑ denotes statistical significance, $P<0.05$; ↑ denotes trend, P value between 0.1–0.05;
↔ denotes not significant

isotropy by assessing corneocyte micromorphology, using SEM on tape-stripped skin samples from six subjects, whom we considered best responders based on clinical assessments. Similar to Fluhr et al., the skin surface isotropy was obtained by evaluating three corneocyte microstructural parameters: cellular clusters at magnification x50, dispersion at x250, and differentiated single cell appearance at x500 (Figure 3A).[16] We found that the UV only zone tended to exhibit a lower SC surface isotropy compared to control at day 1 and day 14 after irradiation, indicating disruption of superficial SC barrier organization patterns (Figure 3A and 3B). At day 1 following UVR, the appearance of both regular clusters and well differentiated corneocytes were significantly reduced in UV only, which the latter tended to be prevented by SPF+Moisturizer routine. By day 14, treatment with SPF or SPF+Moisturizer routine significantly preserved the appearance of well differentiated cornecoytes comparable to control, while weakly differentiated cells persisted in UV only (Figure 3C and 3D). Together, these results suggest that the SPF+Moisturizer routine tended to be most effective in maintaining SC barrier morphological features after UV exposure.

FIGURE 2. Following UV exposure, treatment with sunscreen and moisturizer alone or in combination improve skin hydration but cause no relevant change in TEWL. Change in (A) skin hydration and (B) TEWL at indicated timepoints for each condition following UV exposure.



*denotes $P<.05$ and # denotes P value between 0.1–0.05 vs UV only.

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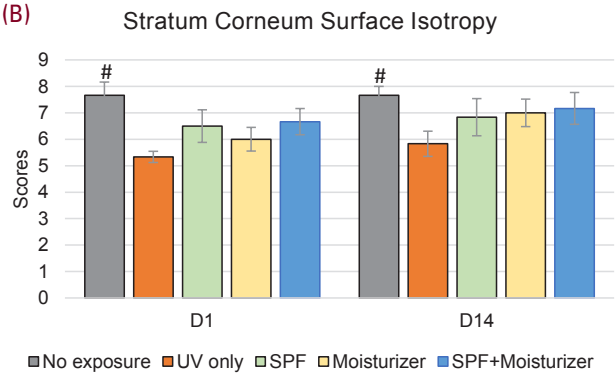
FIGURE 3. Following UV exposure, treatment with sunscreen and moisturizer alone or in combination tend to promote regular stratum corneum (SC) surface isotropy by maintaining normal appearance of differentiated superficial corneocytes. (A) SC surface isotropy scores observed between conditions at day 1 and day 14 post UV, (B) resulting from the sum of individual scores obtained after evaluation of clusters (x50), dispersion (x250) and differentiated single cells appearance (x500). (C) Representative scanning electron images of superficial SC corneocytes obtained by tape-stripping at day 14 post UV for each condition at magnification x500, scale bars = 50 µM. Arrows pointing to cells appearing weakly differentiated. (D) Mean scores of differentiated single cells appearance observed between conditions at day 14 (x500) post UV.

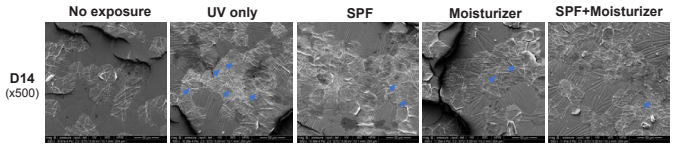
(A)

	Clusters Appearance (x50)		Dispersion Form (x250)		Differentiated Single Cells Appearance (x500)		SC Surface Isotropy (sum score)	
	D1	D14	D1	D14	D1	D14	D1	D14
No exposure	2.67*	2.5	2.33	2.5	2.67*	2.67*	**7.67#**	**7.67#**
UV only	1.67	2.33	2	1.83	1.67	1.67	**5.34**	**5.83**
SPF	2.17	2.17	2.17	2	2.17	2.67*	**6.51**	**6.84**
Moisturizer	2.17	2.5	2	2.17	1.83	2.33#	**6.00**	**7.00**
SPF+Moisturizer	2.17	2.17	2.17	2.5	2.33#	2.5*	**6.67**	**7.17**

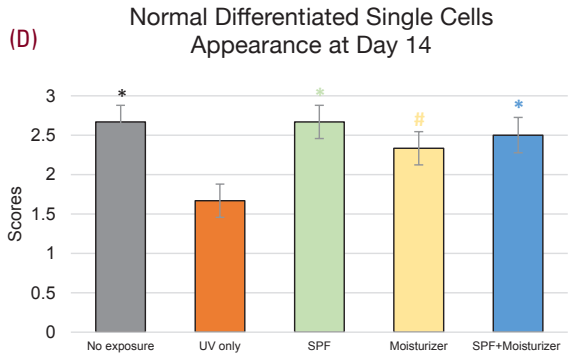
(B)



(C)



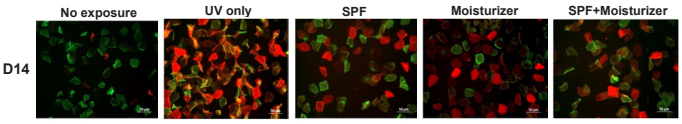
(D)



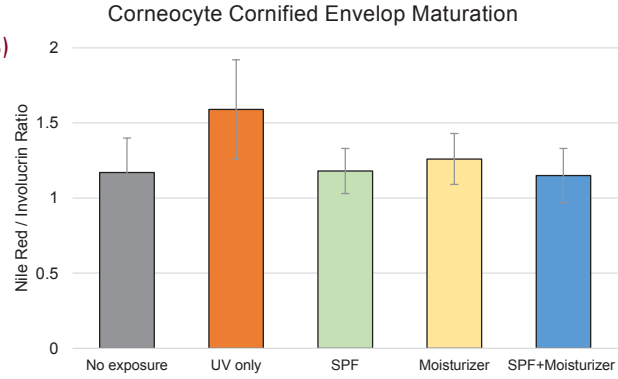
*denotes $P<.05$ and # denotes P value between 0.1–0.05 vs UV only.

FIGURE 4. UV exposure tends to alter corneocyte cornified envelop (CE) maturation, which is minimized by treatment with sunscreen and moisturizer alone or in combination. (A) Representative images of double staining patterns for each treatment at day 14 post UV of corneocyte CE maturation with Nile red (red) and antiinvolucrin (green); scale bars = 50 µM. (B) Quantification of Nile red/Involucrin ratio between conditions at day 14 post UV.

(A)



(B)



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To identify the possible mechanism of UV-induced superficial SC barrier alterations, we investigated whether UVR disrupts corneocyte cornified envelope (CE) maturation properties in the same six subjects. Double staining with Nile red and anti-involucrin revealed no clear trend at day 1 (data not shown). By day 14, UVR tended to stimulate CE maturation (increase in Nile red) in UV only zone, while treatment with SPF or Moisturizer alone or in combination tended to reduce response comparable to control (Figure 4A and 4B). However due to the variation in small sample size, no statistically significant difference was detected.

DISCUSSION

Due to their benefits in promoting skin barrier strength and repair, incorporation of SC lipids into formulas has become increasingly popular across the skincare field.[17] Since our skin is constantly exposed to UVR, it is crucial to delineate its influence on skin barrier, plus to assess the potential benefits of barrier-enforcing lipids formulations for solar protection. Here, we demonstrate the clinical efficacy of a ceramide-containing sunscreen and moisturizer routine in preventing UV-induced skin surface barrier changes.

Solar radiation leads to an immediate skin inflammatory response followed by a protective process, which clinically manifest as erythema and hyper-pigmentation respectively.[18] We showed that treatment with ceramide-containing sunscreen alone or in combination with moisturizing cream prevented the initial erythema response, as well as reduced skin darkening at all timepoints compared to UV only and moisturizer alone (Figure 1A and 1B). The protective effects provided by the ceramide-containing sunscreen is likely due to its UV-filter capability, as the photoprotective clinical efficacy of sunscreens against UV-induced cutaneous responses are well documented.[19] Although the exact mechanism awaits further investigation, growing evidence indicates that CERs also have anti-pigmentation properties.[20] Future studies are needed to expand on these premises and determine the mechanisms of CERs depigmentation capabilities, and added benefits when combined with UV filters.

UV is shown to disrupt skin barrier integrity by increasing TEWL, decreasing skin hydration, promoting SC and epidermal thickness, plus changing skin lipids and proteins levels and structures.[4,6,21] Despite the differences in study conditions, the variation of UVR effects on skin barrier-related endpoints remains poorly understood. Haratake et al, demonstrated that UVR (7.5 MED) can lead to a delayed impaired barrier response followed by rapid recovery, which was dependent on epidermal hyperproliferation and inflammation.[22] Subsequently, Holleran et al, reported that the same UV dose after 24 hours caused incidence of damaged lamellar bodies (LBs) only at the stratum granulosum (SG) and SC interface, which contributed to the delayed in abnormal barrier permeability and no change in TEWL. Following 72 hours, he observed a deficient lamellar membrane in the lower SC and an increase in impaired LBs at SG/SC interface, causing elevated TEWL and compromised barrier. By 120 hours, there was a hyperproliferative response promoting thickening of the SG and arrival of normal lamellar membranes in the lower SC, which in turn resulted in the restoration of the epidermal barrier.[23]

In our study, UVR (2 MED) did not cause a drastic change in either TEWL nor hydration (Figure 2A and 2B), which could be attributed to the skin's ability to delay barrier deficiency and rapidly recover from superficial damage. Nevertheless, treatment with ceramide-containing sunscreen in combination with moisturizer (SPF+Moisturizer) improved skin hydration over time, indicating that the skin water content, which is essential for maintaining barrier function, was both maintained and ameliorated. Moreover, we observed that UVR tended to alter skin surface organization patterns and promote corneocyte maturation (Figure 3 and 4). Out of the three corneocyte microstructural parameters evaluated, UVR significantly increased the appearance of weakly differentiated cells in untreated skin, which persisted up to day 14 and was prevented by treating with the sunscreen or moisturizer alone or in combination (Figure 3C and 3D). This phenomenon is consistent with the ability of UVR to decrease SC cohesion by altering intracellular lipids and corneodesmosomes to compromise barrier integrity.[4] Altogether, our findings suggest that an increase in corneocyte maturation was a result of some degree of UV-induced skin barrier damage, disrupting superficial SC morphology. Thus, increased SC turnover or epidermal hyperplasia, as shown in prior studies, are all compensatory mechanisms that the skin barrier utilizes to adapt in response to UV stress to prevent subsequent damage.[21–23] Our results indicate that a skincare routine combining a ceramide-containing sunscreen and moisturizer may prevent early UV-induced skin barrier damage and the consequent skin physiological alterations. However, some limitation should be noted. We were unable to compare the efficacy of our ceramide-containing products with non-ceramide containing sunscreen and moisturizer due to limited test sites on subjects. Future studies will expand on our findings and determine the exact mechanism of CERs capabilities, plus added benefits when combined with UV filters and other ingredients for promoting skin barrier health in response to UV-induced stress.

CONCLUSION

Collectively, our results show that a ceramide-containing sunscreen and moisturizer routine protects against UV-induced skin surface barrier changes by preventing erythema and hyperpigmentation, improving skin hydration, and maintaining normal superficial skin cells morphology and turnover. In addition to improving appearance of lesions and minimizing

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skin irritation, our findings highlight that delivering skin-identical SC lipids could add benefits to patients' daily routine by strengthening the barrier and improving skin health overall against chronic sun exposure.

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