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Disclosure of Commercial Support

This supplement to the Journal of Drugs in Dermatology is supported by SkinMedica, an Allergan Company.
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ABSTRACT

For more than a century, solar radiation has been known to contribute significantly to the extrinsic aging of skin. Until recently, this was almost exclusively attributed to the photodamage caused by ultraviolet (UV) light. However, a growing body of evidence now indicates that both infrared (IR) and visible light may also contribute to extrinsic skin aging. Infrared radiation, comprised of IR-A, IR-B, and IR-C, accounts for 54.3% of the total solar radiation reaching the skin. Studies have shown that IR radiation is also responsible for skin aging. Thus, IR-A radiation regulates hundreds of genes in skin, with roles in extracellular matrix (ECM) homeostasis regulation, apoptosis, cell growth, and stress responses. IR-B and IR-C radiation are primarily responsible for the increase in skin temperature associated with solar exposure, and are implicated in heat-related skin destruction of collagen and elastin, which is characterized by an increase in the expression of matrix metalloproteinases (MMPs). The contribution of visible light to photoaging is less well understood; however, some preliminary indication associates visible light with the upregulation of MMPs' expression, DNA damage, and keratinocyte proliferation. Interestingly, the common denominator that links skin damage to the different solar wavelengths is the enhanced production of reactive molecule species (RMS) and therewith increased oxidative stress. SkinMedica® Total Defense + Repair (TD+R; SkinMedica Inc., an Allergan company, Irvine, CA) is a “superscreen,” which combines broad spectrum UV protection with a unique blend of antioxidants (SOL:IR Advanced Antioxidant Complex™) that provide protection from IR radiation while promoting skin repair. Preclinical studies have indicated that TD+R SPF34 prevents the formation of UV-induced sunburn cells and cyclobutane pyrimidine dimers while preserving or improving the expression of ECM genes. In addition, it prevents IR-A-triggered fragmentation of elastin fibers and expression of MMP-1. Initial clinical studies indicate that TDR+R SPF34 reduces the increase in surface temperature seen with IR radiation. A significant improvement in the appearance of lines and wrinkles was reported as early as week 2 in patients using TDR+R SPF34. In summary, we observed that the unique blend of antioxidants present in TD+R acts in harmony with SPF active ingredients, expanding solar protection beyond UV radiation and counterbalancing the deleterious effects of free radicals on skin cells by promoting endogenous repair.

J Drugs Dermatol. 2015;14(suppl 7):s3-s11.

INTRODUCTION

The relationship between sun exposure and skin damage has long been established. Reports from as early as the 19th century described photoaging, photodistributed dermatosis, and a high incidence of keratosis and skin cancer in individuals who spent significant time outdoors.1,2 The first study identifying a causal link between a specific wavelength of light and skin damage was published in 1922, suggesting that wavelength in the ultraviolet-B (UVB) range were primarily responsible for sunburn.3 Despite this early interest, the field of photodermatology did not develop significantly until the late 1960's, when Kligman's landmark report was published differentiating extrinsic ageing (photoaging) from intrinsic aging.4 At this point, it was still believed that UVB was the wavelength responsible for skin damage, a concept that was not challenged until 1977 when Kumakiri et al identified ultrastructural changes in skin as a result of repeated exposure to ultraviolet-A (UVA) radiation.5

Studies conducted during the late 20th century focused on the deleterious effects of UVA and UVB radiation on the skin, with little or no consideration of the effects caused by other wavelengths.
Infrared Radiation

Previously, the negative effects of solar light on human skin were primarily attributed to wavelengths in the UVB and UVA range. However, recent research has shown that other solar wavelengths, such as IR and visible light, may also play a key role in extrinsic skin aging. Human skin is predominantly exposed to IR radiation, which accounts for 54.3% of total solar light. Infrared radiation is comprised of IR-A (760 nm - 1,400 nm), IR-B (1,400 nm - 3,000 nm), and IR-C (3,000 nm - 1 x 10^4 nm). Among them, IR-A accounts for 30% of total solar radiation and has the capacity to penetrate deeper into the skin, reaching subcutaneous tissues (Figure 1). Nowadays, there is compelling evidence that associates solar IR-A radiation with premature aging and the progression of malignancies. Interestingly, for many years IR-light based therapies have been used clinically to promote wound healing, protect muscles from stress, and reduce proinflammatory cytokine and chemokine production. The apparent dichotomy of IR-A and its effect on the skin (good or bad? friend or foe?) is explained by the capacity to control the intensity, time of exposure, and heat production during clinical exposure to IR-A.

IR-A regulates proximally 600 genes in human skin that are involved in ECM homeostasis, apoptosis, cell growth, and stress responses. While the mechanisms by which this occurs are highly complex, it is thought that many of the pathological effects of IR-A are attributable to the altered function of mitochondria, as the cytochrome c oxidase from complex IV acts as its photo-acceptor. Interestingly, it has been shown that simultaneous exposures to multiple wavelength of low energy light (ie, visible and near IR radiations) also modulated cell metabolism and gene expression, indicating that ratios of different solar rations may impact skin premature aging. IR-A–induced mitochondrial changes (ie, increase in mitochondrial reactive oxygen species [ROS] production, decreased adenosine triphosphate [ATP] synthesis, and enhanced permeability) are responsible for the activation of a retrograde signaling pathway that can trigger activation of mitogen-activated protein kinases (MAPKs) and caspasess (apoptosis). MAPK pathways play a critical role in controlling the expression of MMPs and therefore ECM destruction. Moreover, studies using different experimental models showed that IR radiation enhanced the deposit of elastotic material in the dermis while decreasing collagen. Epidermal hyperplasia/thickening, increased senescent marker expression (ie, telomerase expression and activity), angiogenesis (by increasing vascular endothelial growth factor [VEGF] production and CD31 positive cells), erythema, and swelling are also characteristics present in IR-radiated skin. Finally, IR-A also triggers a significant decrease in antioxidant capacity in the skin (specifically by destroying carotenoids such as β-carotenes and lycopene), as well as the activation-recruited mast cells (MCs), enhance oxidative stress and inflammation, promoting premature aging.

"We observed that the unique blend of antioxidants present in Total Defense + Repair acts in harmony with SPF active ingredients, expanding solar protection beyond ultraviolet radiation."
Heat-Thermal Aging

Solar IR radiation transmits heat energy that is responsible for raising skin temperatures to levels close to or higher than 40°C. Chronic increases in skin temperatures are associated with "erythema ab igne," a pathology that is characterized by reticular pigmentation of the skin and by the presence of dermal solar elastosis similar to that seen in photoaged skin. Thus, heat-linked premature aging of the skin has been reported on baker’s arms and on the faces of glass blowers, supporting the concept of thermal-aging or premature aging being triggered by heat. IR-associated increase in temperature is mainly associated with IR-B and IR-C, which are absorbed by the epidermis.41

Heat-related skin damage is characterized by an increased expression of MMPs, more specifically MMP1, MMP-3, and MMP-12, resulting in the destruction of collagen and elastin.43,44 In addition, heat also promotes dermal expression of tropoelastin while decreasing fibrillin-1 levels, resulting in the accumulation of elastotic material.44 Increased ROS production by heat is

![Image](https://via.placeholder.com/150)

**FIGURE 1.** Solar-aging: combination of photoaging, infrared aging, visible aging, and thermal aging: 1+1+1+1=100, synergistic implications. The deleterious effects of solar radiation on human skin are the combination of UVR, visible light, IR, and heat. Synergistic effects of these factors on skin aging cannot be discarded and require further investigation. Increased formation of reactive molecule species (RMS) or free radicals is a common pathway that becomes activated by the different components of solar radiation and heat, though the initial place of RMS generation (membrane, nuclei, mitochondria, or cytosol), as well as the type of reactive molecule formed, may differ. Ultraviolet radiation – UVA (320 nm - 400 nm) and UVB (290 nm - 320 nm) – accounts for approximately 6.8% of solar radiation. UVC (200 nm - 290 nm) is fully blocked by the atmosphere. UVB penetrates only at the epidermal level, while UVA affects both the dermis and epidermis. Visible light (400 nm - 760 nm), the portion of solar electromagnetic radiation that is visible to the human eye, accounts for 38.9% of total solar radiation. Visible light penetrates into the dermis and generates heat upon absorption. Infrared radiation accounts for 54.3% of total solar radiation and is formed by IR-A (760 nm - 1,440 nm), IR-B (1,440 nm - 3,000 nm), and IR-C (3,000 nm - 1 mm). IR-A penetrates deeply, reaching the epidermis (35%), dermis (48%), and subcutaneous tissues (17%). IR-B reaches as deeply as IR-A, but the main part of it (72%) is absorbed by the epidermis (20%) and 8% are absorbed by the dermis and subcutaneous tissues, respectively. IR-C is fully absorbed by the epidermis.
mainly due to the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, and the mitochondrial electron transport system, and it is responsible for protein and DNA oxidation. Increase in skin temperatures is also associated with chronic inflammation and a pro-angiogenic environment characterized by an increased VEGF to thrombospondin (TSP)-1 and 2 ratio. Finally, heat-activation of transient receptor potential vanilloid-1 (TRPV-1) mediates the expression of MMP-1, opening a potential role for TRPV-1 inhibitors to be used to prevent heat-induced skin aging.

Visible Light

The visible part of the solar spectrum is used for general illumination and is defined by the electromagnetic radiation that is visible to the human eye (400 nm - 760 nm). Visible light accounts for the remaining 38.9% of the solar radiation reaching the earth’s surface, and is able to penetrate the dermis and generate heat after being absorbed. While there is now substantial evidence to indicate that UV, IR, and heat all influence solar-aging, the contribution of visible light to skin damage is less well understood, due in part to the lack of light sources that emit in the visible spectrum (without UV or IR contamination).

Recent experiments have shown that visible light can increase the production of ROS, stimulate the production of pro-inflammatory cytokines, and upregulate the expression of MMP-1 in humans. In addition, a potential role of visible light in DNA damage has been suggested by Kielbassa et al, who estimated that 10% of the total DNA oxidation is associated with

FIGURE 2. Pretreatment of Epiderm-FT tissues with Total Defense + Repair prevents sunburn cell formation (representative histological results). In brief, stabilized Epiderm-FT tissues were treated with TD+R SPF34 10 mins before radiation. Formulation was left during UVB radiation (200 mJ/cm², equivalent to 5MED) and tissues were allowed to further recover for a total time of 6, 16, and 24 hours after UVR. As expected, UVB radiation induced the formation of sunburn cells (SBCs) (apoptotic keratinocytes, white arrows). The number of SBCs increased as untreated tissues recovered from UVR radiation. Pre-treatment with TD+R SPF34 resulted in the prevention of SBC formation. n=3 in each condition.

FIGURE 3. Treatment with Total Defense + Repair SPF34 prevents UVB-dependent cyclobutane pyrimidine dimers formation in a full thickness reconstituted skin model. Pyrimidine dimers are molecular lesions in the DNA produced via photochemical reactions. Ultraviolet radiation is the main source of pyrimidine dimer formation, which are bulky DNA adducts. The most common CPDs include thymine dimers, thymine-thymine dimers, and 6,4 photoproducts. These are mutagenic lesions that alter the structure of DNA and inhibit polymerases arresting replication. CPDs need to be removed and repaired to preserve cellular integrity. A representative immuno-staining that shows detection of CPDs in Epiderm-FT tissues after UVR-radiation is shown in this figure. Tissues were pretreated with TD+R SPF34 as described in Figure 2, and allowed to recover for 24 hours after UVR radiation. Histological analyses were performed on formalin-fixed paraffin embedded (FFPE) samples using anti-thymine dimer mouse monoclonal antibody (Kamiya Biomedical Company, Seattle, Washington, USA). n=3 in each experimental group.
FIGURE 4. Pretreatment with Total Defense + Repair SPF34 prevents deleterious effects of UVB-radiation on ECM and superoxide dismutase 1 gene expression in the dermis. Epidermal-TF tissues were pretreated with TD+R SPF34 as described in Figure 2 and allowed to recover for 24 hours after UVB radiation. The dermis and epidermis were physically separated, and gene expression was assessed using commercially available TaqMan® labeled primers. Results showed a prevention of deleterious effects of UVB on the expression of collagen type I (COL1A1), collagen type 3 (COL3A1), elastin (ELN), and superoxide dismutase 1 (SOD1), n=6 in each experimental group. (*) P<.01 with respect to control and UVR groups.

FIGURE 5. Prevention of IR-A–associated disruption of elastin fibers by pretreatment with SOL-IR Advanced Antioxidant Complex. Human skin explants (4-11mm) were obtained from an abdominoplasty (Caucasian female 48 years old) and treated with SOL-IR Advanced Antioxidant Complex (2 µl/cm²) on day 0 to day 6. On day 5 the tissues were irradiated with IR-A (720 J/cm²). The surface temperature of the explants was maintained at or below 39°C. Tropoelastin immunostaining was performed on frozen samples using a monoclonal antibody from Chemicon (Chemicon International Inc., Billerica, Massachusetts, USA) followed by a secondary FITC-conjugated antibody from Invitrogen (Invitrogen™, Carlsbad, California, USA). Figure 5 shows representative immunostaining of tropoelastin in the papillary dermis and upper reticular dermis. An acute (24 hour) decrease in tropoelastin staining was observed in the IR-A group compared with the control group (non-radiated, non-treated). A significant fragmentation of elastin fibers in the upper reticular dermis was also observed in response to IR-A radiation at the same time point. Pretreatment with SOL-IR Advanced Antioxidant Complex prevents in part the deleterious effects of IR-A on human skin explants.

One interesting hypothesis suggests a role of visible light on skin pigmenary changes. Three decades ago, Kollias and Sague showed that pigmenary changes could occur in response to near-IR light in the absence of ultraviolet radiation (UVR). Porges et al demonstrated that exposure to visible light (385 nm - 690 nm) triggered acute and fading erythema on skin types II and III, which later resulted in darkening of the skin that remained for the duration of the experimental protocol (10 days). More recently, Mahmoud et al showed that melanin-competent skin types (types IV-VI) respond to visible light with pigment formation that differs from the UVA1–induced darkening. Interestingly, these authors showed migration of melanin from basal cells into the upper layers of the epidermis in response to visible light. Though further investigation is required to assess the role of melanin in visible light–induced pigmentation, it is important to remark that this pigment has the capacity to absorb visible light, generating heat that can lead to deep dermal vessels dilation, erythema, and inflammation, further aggravating potential pigmentary changes. In agreement, Chiarelli-Neto et al showed that UVB–induced melanin can act as a visible light photo-sensitizer, leading to singlet oxygen (¹O₂) formation, which can interact with proteins, nucleic acid, and membranes to trigger cell damage.

Antioxidant Protection and Repair

Antioxidants are widely used in the cosmetic industry due to their capacity to prevent or minimize the oxidation of molecules. Though oxidation of molecules is common and essential for the cellular functioning, it can also result in damage to key structures. Aside from oxidation of DNA, lipids, and proteins, overproduction of RMS modulates cellular regulatory mechanisms and signal transduction pathways, metabolism, inflammation, immune system activation, and apoptosis. To prevent cellular or structural damage due to unwanted or uncontrolled oxidations, all living organisms maintain complex systems of multiple types of antioxidant, which are the natural defense against free radicals or RMS. Antioxidants perform their function by becoming oxidized themselves, and they act also as pro-oxidants under certain circumstances. This capacity of antioxidants to play “in favor of or against” our skin health and integrity needs to be taken into consideration when designing cosmetic products to provide the maximum benefits in the absence of potentially harmful effects.

In the skin, an increase in oxidative stress, which is characterized by enhanced production of RMS, is the main cause
of molecule oxidation, endogenous antioxidant consumption/inactivation, and premature aging. A decrease in skin endogenous antioxidant levels occurs in response to environmental factors (ie, solar radiation, pollution, smoking, diet, stress, inactivity, etc.) and endogenous factors (ie, normal metabolism, mitochondria-produced free radicals, chronological aging, activation of immune responses, inflammation, etc).

Either way, a net decrease in the skin antioxidant capacity flips the physiological balance toward premature or accelerated aging.

An interesting function of antioxidants is linked to their potential capacity to restore or prevent skin damage in a timeline-independent manner. Therefore, topical antioxidants can repair past damage of the skin by controlling undergoing chronic inflammation, promoting ECM repair, decreasing activation of melanocytes, and controlling angiogenesis. They can neutralize present damage by preventing (or minimizing) RMS formation before these molecules can negatively impact ECM production or levels, immune and inflammatory responses, pigment formation, and cellular viability. Finally, they can prevent future skin damage by preserving skin homeostasis and by increasing antioxidant capacity in the skin.

**Current Practice**

Currently, sunscreens play an important role in maintaining the health of the skin by providing “broad spectrum” protection against the harmful effects of UV radiation (UVA 320 nm - 400 nm, and UVB 290 nm - 320 nm). To achieve protection against these wavelengths, sunscreens combine several ingredients (chemical or physical actives) such as PABA derivatives, salicylates, cinnamates (octylmethoxycinnamate and cinoxate), benzophenones (such as oxybenzone and sulisobenzone), avobenzone, titanium dioxide, or zinc oxide.

However, current “broad spectrum” protection does not protect human skin from 94.2% of solar radiation (comprised of
visible and IR light), and nor does it prevent heat accumulation damage. Thus, none of the commercially-available sunscreens (that can block wavelengths up to 380 nm) are able to block 100% of UVR. For example, SPF 15 filters out approximately 93% of all incoming UVB rays. SPF 30 and SPF 50 keep out 97% and 98% of total UVR. The magnitude of the UVB radiation that escapes UV-filters may seem negligible, but can make a difference if the person has light-sensitive skin or a predisposition to skin cancer.

"Initial clinical-use testing of Total Defense + Repair on subjects with moderate to severe facial photodamage demonstrated visible improvements in lines and wrinkles after 4 weeks of once-daily use."

**Total Defense + Repair**

Although different wavelengths of solar radiation (UVA, UVB, IR, visible) damage human skin by activating different pathways, they share as a common mechanism the generation of RMS and oxidative stress (Figure 1). Therefore, it is logical to assume that more realistic broad solar protection can be accomplished by the combination of SPF active ingredients and antioxidants. A key consideration for boosting SPF protection is to select the appropriate blend of antioxidants. Specifically, antioxidants should exhibit stability in response to solar radiation and to heat, and should also show high potency to neutralize RMS activity while promoting repair of damaged structures.

Inspired by the need to provide patients with a more comprehensive solar protection, SkinMedica® created Total Defense + Repair (TDR+R), a rejuvenating superscreen that represents a new generation in solar skin care protection. TDR+R combines SPF actives providing UVA and UVB broad spectrum protection with a proprietary blend of antioxidants (SOL-IR Advanced Antioxidant Complex™) that provides IR-A and heat protection while minimizing inflammation and promoting skin repair. Efficacy testing of TDR+R was evaluated using *in vitro*, *ex vivo*, and clinical testing.

**In Vitro Testing**

Protection against UVB radiation was tested using Epiderm-full thickness (Epiderm-FT™); MatTek Corporation, Ashland, MA, USA) radiated with a UVB light dose equivalent to 5 MED (200 mJ/cm²). As expected, this dose of UVB resulted in the formation of sunburn cells (SBCs) and cyclobutane pyrimidine dimers (CPDs) in radiated but untreated tissues (Figures 2 and 3). Pretreatment of tissues with TDR+R SPF34 (2 μl/cm²) 10 minutes before UVB radiation prevented both SBC and CPD formation, as well as other histological changes associated with UVB radiation. Interestingly, pretreatment with TDR+R SPF34 also helped prevent UVB-mediated down regulation of ECM genes (Figure 4).

**Ex Vivo Testing**

IR-A protection was evaluated using abdominal human skin explants (Figure 5). Human tissues were pretreated with SOL-IR Advanced Antioxidant Complex (2 μl/cm²) for 5 days before being radiated with a single dose of IR-A (720 J/cm²). We observed a significant alteration of tropoelastin distribution and abundance in both papillary and upper reticular dermis response to IR-A (24 hours after IR-A radiation). Pretreatment with SOL-IR Advanced Antioxidant Complex partially prevented these alterations (Figure 5). Moreover, tissues treated with this unique blend of antioxidant do not differ from the control tissues (non-radiated, non-treated) after 4 days IR-A radiation (data not shown).

**Clinical Testing**

To assess the ability of TDR to protect against IR-induced heat accumulation, a proof of concept clinical study was conducted. Two test sites (2 cm x 5 cm), including untreated control and TDR, were randomly assigned to designated locations on the back of each subject. TDR+R SPF34 was applied approximately 15 minutes prior to IR radiation exposure. Subjects were positioned 33 cm away from the IR source (Hydrosun® 750; Hydrosun GmbH, Mullheim, Germany), which has an emission wavelength range of 760 nm to 1,400 nm. The test sites were exposed in 30 minute increments, where the surface skin temperature was recorded every 30 minutes. Infrared thermograph images were taken every 30 minutes to capture the skin’s surface temperature (ICI 9320 P-Series Thermal Camera; ICI Infrared Cameras Inc., Beaumont, Texas, USA) at baseline and at minutes 30, 60, 90, 120, and 150. Test sites treated with TDR consistently provided protection against IR-induced heat compared with untreated sites at all follow-up time points (Figure 6). The mean temperature for TDR test sites was significantly lower than untreated at 90 minutes (*P*<0.039) and trended toward significance at other time points.

Initial clinical-use testing of TDR+R SPF34 on subjects with moderate to severe facial photodamage demonstrated visible improvements in lines and wrinkles after 4 weeks of once-daily use (Figure 7). In a separate clinical study, significant improvements in lines and wrinkles, skin tone unevenness, and texture were observed after only 2 weeks of twice-daily use in subjects with moderate to severe facial photodamage (all *P*<0.03). These initial results suggest that the antioxidants included in TDR work beyond providing protection against solar radiation, and may also work on repairing existing photodamage.
CONCLUSION

The deleterious effects of solar radiation are not linked exclusively to UVR. In vitro and clinical studies have shown that visible and IR radiations, as well as heat accumulation, are able to activate different signal transduction pathways, resulting in enhanced oxidative stress and premature aging. Chromophores for solar lights are localized in different cellular compartments, (ie, IR-A is mitochondrial cytochrome c complex, UVA is lipid in the biological membranes, and UVB is DNA in the nuclei), which strongly suggests a synergistic effect among these different types of radiation (UV-V-IR-visible heat). Thus, a sensitive approach to providing an efficacious and comprehensive solar protection is to generate SPF active ingredients with potent and efficacious antioxidants. TDR has a blend of antioxidants and special ingredients that complements SPF ingredients, redefining total (broad) solar protection. These antioxidants are the product of breakthrough technology, scientific research, and innovation, providing the next generation of multifunctional skin care products. SOL-IR Advanced Antioxidant Complex acts in harmony to diminish the signs of aging, providing an active superscreen effect that counterbalances the deleterious effects of free radicals on skin cells whilst promoting endogenous repair.

DISCLOSURES

Virginia L. Vega, Rahul Mehta, and Elizabeth T. Makino are employees of SkinMedica, an Allergan Company. David McDaniel was a MAB for Juvederm Voluma and has performed other consulting work for Allergan and SkinMedica.

ACKNOWLEDGMENTS

We would like to thank Kuniko Kadoya PhD and Robin Gnanan for providing us with unpublished data, and Samantha Widdicombe for her administrative support.

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