3-1-2022

Impact of visible light on skin health: The role of antioxidants and free radical quenchers in skin protection

Henry W. Lim
Henry Ford Health, hlim1@hfhs.org

Indermeet Kohli
Henry Ford Health, ikohli1@hfhs.org

Eduardo Ruvolo

Ludger Kolbe

Iltefat H. Hamzavi
Henry Ford Health, ihamzav1@hfhs.org

Recommended Citation

Lim HW, Kohli I, Ruvolo E, Kolbe L, and Hamzavi IH. Impact of visible light on skin health: The role of antioxidants and free radical quenchers in skin protection. J Am Acad Dermatol 2021.

Impact of visible light on skin health: The role of antioxidants and free radical quenchers in skin protection

Henry W. Lim, MD,[a] Indermeet Kohli, PhD,[a] Eduardo Ruvolo, MS,[b] Ludger Kolbe, PhD,[b] and Iltefat H. Hamzavi, MD[a]

Detroit, Michigan and Morristown, New Jersey

Until recently, the primary focus of photobiology has centered on the impact of UV radiation on skin health, including DNA damage and oncogenesis; however, the significant effects of visible light (VL) on skin remain grossly underreported. VL has been reported to cause erythema in individuals with light skin (Fitzpatrick skin types [FSTs] I-III) and pigmentary changes in individuals with dark skin types (FSTs IV-VI). These effects have importance in dermatologic diseases and potentially play a role in conditions aggravated by sun exposure, including phototoxicity in patients with FSTs I to III and post-inflammatory hyperpigmentation and melasma in patients with FSTs IV to VI. The induction of free radicals, leading to the generation of reactive species, is one driving mechanism of VL-induced skin pathologies, leading to the induction of melanogenesis and hyperpigmentation. Initial clinical studies have demonstrated the effectiveness of topical sunscreen with antioxidant combinations in inhibiting VL + UV-A1-induced erythema in FSTs I to III and reducing pigmentation in FSTs IV to VI. Antioxidants may help prevent the worsening of pigmentary disorders and can be incorporated into photoprotective strategies. It is essential that dermatologists and the public are aware of the impact of VL on skin, especially in patients with skin of color, and understand the available options for VL protection. (J Am Acad Dermatol 2022;86:S27-37.)

Key words: antioxidants; free radicals; photoprotection; visible light.

VISIBLE LIGHT SPECTRUM AND VISIBLE LIGHT SOURCES

Electromagnetic radiation from the sun is the major source of visible light (VL) exposure on our skin. VL encompasses the electromagnetic radiation visible to the human eye, spanning from 400 to 700 nm of the electromagnetic radiation, and can be divided by color and wavelength (Fig 1)[1-3]; however, it is imperative to understand that the VL wavelength cutoffs are arbitrary and the VL spectrum is a continuum from the tail end of the long-wavelength UV-A spectra.[4] Recent data demonstrate the synergistic effects between VL and UV-A1 on erythema and pigmentation compared to those induced by pure VL; however, although both UV-A1 and VL can induce pigmentation in dark skin types, VL-induced pigmentation is darker and more sustained than UV-A–induced pigmentation.[4,5] One major issue in the underreporting of VL-induced pathologies is the use of VL sources with different spectral outputs for VL phototesting due to a lack of testing guidelines currently available.[4]

Other sources of VL include light-emitting diodes, flash lamps, computers, televisions, and cell phones.[6,7] Of importance to skin health, violet-blue light, often referred to as high-energy VL, spans from 400 to 500 nm on the VL spectrum and appears to have the most significant biological effects on the skin when compared to red light, which spans from 620 to 700 nm.[6-8] It is important to note that the relative intensity of blue light (420-490 nm) from computer screens, televisions, and cell phones is 99 to 1000 times less than that of sunlight and has not shown worsening in patients with melasma. In a controlled study, Duteil

From the Photomedicine and Photobiology Unit, Department of Dermatology, Henry Ford Health, Detroit, Michigan[a] and Beiersdorf, Inc, Morristown, New Jersey.[b]

This article is published as part of a supplement sponsored by Beiersdorf Inc.

Funding sources: Supported by an unrestricted educational grant from Beiersdorf Inc.

IRB approval status: Not applicable.

Accepted for publication December 13, 2021.

Reprints not available from the authors.

Correspondence to: Henry W. Lim, MD, Henry Ford Medical Center - New Center One, 3031 West Grand Boulevard, Suite 800, Detroit, MI 48202. E-mail: hwl719@gmail.com.

Published online December 20, 2021.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2021.12.024

et al[9] showed that at a 20-cm distance from melasma lesions, the maximized use of a high-intensity computer screen for 8 hours per day during a 5-day period did not worsen melasma lesions.

IMPACT OF VL ON SKIN HEALTH: THINKING BEYOND UV-A AND UV-B

VL skin penetration

Decades of research have focused on the effects of UV radiation on skin health, centered initially on the role of UV-B in sunburn and DNA dimer formation, with recent advancements regarding UV-A's role in the generation of oxidative reactive species and immunosuppression.[1,4,10,11] Only recently have we begun to understand the impact of VL on skin pathologies that leads to the induction of oxidative stress, erythema, melanogenesis, and hyperpigmentation.[1,4,6,10-15]

CAPSULE SUMMARY

- The impacts of visible light on skin health, including the induction/exacerbation of hyperpigmentation and melanogenesis, are summarized.
- The role of endogenous and novel exogenous antioxidants and oxygen radical scavengers aimed at reducing the effects of visible light damage to skin health are highlighted.

VL's effects on skin are associated with a greater penetration depth of this waveband into the layers of the skin relative to UV radiation. Red light has been shown to penetrate the full thickness of the epidermis and dermis, reaching the subcutaneous adipose layer,[16-21] demonstrating the proportionality of the wavelength to the depth of penetration and its inverse relationship with energy,[6,22,23] while blue light, with its higher energy, has less penetration. The penetration depth for a 63% reduction in incident intensity ranges from 90 to 230 microns for 400 to 500 nm and from approximately 0.5 to 1 mm for the longer VL wavelengths in Caucasian skin (Fig 2). Of note, the penetration depth decreases with an increase in pigmentation.[6,16,24]

VL molecules in skin

The depth of VL penetration is influenced by the reflection, scattering, and absorption mediated not only by the skin's physical barrier but also by the VL chromophores in the skin and the Fitzpatrick skin type (FST).[6,16-18,25] The primary VL-scatter and absorption molecules in the skin include hemoglobin, melanin, keratin, bilirubin, carotene, lipids, and other structures, including cell nuclei and filamentous proteins. The individual contributions from secondary chromophores may be considered separately.[7,16-18,25] Melanin and keratins are the primary VL absorbers and scatterers in the epidermis, and while hemoglobin is the dominant absorber, collagen is the major VL scatter in the dermis.[26] Melanin in human skin exists in 2 forms, eumelanin and the sulfur-containing pheomelanin (found mostly in fair-skinned individuals with red hair).[6,10,27-29] Melanin's absorption spectrum ranges from 200 to 900 nm, with the peak absorption varying based on melanin moiety.[1,6,10,30,31] Keratins are the filamentous proteins of the epidermis and the major constituent of this layer; thus, the primary sources of VL scatter, while collagen is the principal filamentous protein of the dermis, occupying 18% to 30% of the layer's volume and serving as this layer's primary source of VL scatter.[25,32] The VL-scatter properties of these 2 filamentous proteins are directly proportional to the fiber diameters and inversely proportional to the wavelengths, in part explaining the difference in penetration depth for blue and red light into the epidermis and dermis.[25,33,34] Hemoglobin, consisting of 4 polypeptide chains, each bound to a molecule of heme, is the dominant absorber of light in the dermis.[25,35] Hemoglobin has a peak absorption of VL in the blue (418 nm) and yellow/orange (542/577 nm) waveband, with the maximum absorption directly related to the erythrocyte concentration.[1,6,25] Opsins (OPNs) are a large group of light-sensitive, G protein–coupled receptors responsible for triggering signaling cascades when activated by various wavelengths of light, including VL, resulting in VL phototransduction.[6,36-38] Identified skin OPN's activation wavelengths range from 380 to 400 nm (OPN4, OPN5) to as high as 557 to 560 nm (OPN-1-LW). Various cell types in the epidermis and dermis, including melanocytes, keratinocytes, fibroblasts, and hair follicle stem cells, have been shown to have opsin receptors.[6,36,38-43] The group of carotenoids in human skin includes α-carotene, γ-carotene, ß-carotene, lycopene, lutein, and zeaxanthin and their isomers.[44,45] The distribution of carotenoids in human skin depends on the areas of skin examined and significantly varies from individual to individual.[44,46] The protective role of carotenoids in the skin centers on the powerful antioxidant capacity of the molecules, especially as quenchers of reactive oxygen species (ROS).[44,47,48]

VL-mediated pathologies/reactions

VL-induced/exacerbated pathologies and reactions include erythema, post-inflammatory hyperpigmentation, melasma, and photodermatoses.[6] In FSTs I to III, VL has been shown to induce immediate

Abbreviations used:

FST: Fitzpatrick skin type
OPN: opsin
RNS: reactive nitrogen species
ROS: reactive oxygen species
VL: visible light

erythema.[49] In FSTs IV to VI, erythema may not be readily apparent clinically; however, recent spectroscopic studies using diffuse reflectance spectroscopy demonstrate immediate and prolonged VL-induced erythema in dark-skinned individuals.[12,14,50] While UV-induced erythema is the result of capillary dilatation in the papillary dermis, VL-induced erythema appears to be the result of the dilatation of vessels of the subpapillary plexus.[50] VL-induced pigmentation, including post-inflammatory hyperpigmentation, is exacerbated and prolonged in patients with FSTs IV to VI as compared to UV-A1—induced pigmentation.[6,50,51] Exposure to VL can induce inflammatory responses, leading to the stimulation of melanocytes, via ROS, resulting in the exacerbation of preexisting hyperpigmentation.[52-54] Melasma, the acquired facial pigmentary disorder observed more frequently in FSTs IV to VI, can be further exacerbated with VL exposure.[55,56] Lastly, VL is the action spectrum of some patients with photodermatoses, including solar urticaria, chronic actinic dermatitis, polymorphous light eruption, and cutaneous porphyrias.[13,50,57]

Free radicals and ROS generated by VL and impact on skin health

Efforts are underway to better understand the underlying mechanisms through which VL impacts skin health, including melanogenesis, inflammation, and DNA damage.[4-6,8,11,12,14,15,49,50,58-60] One important contributing factor is the VL induction of free radicals and ROS, leading to a cascade of events altering skin health, including the induction of proinflammatory cytokines, matrix metalloproteinases, and melanogenesis.[4-6,8,11,12,14,15,49,50,58-60] Until recently, the generation of reactive species, including ROS and reactive nitrogen species (RNS), was attributed exclusively to UV radiation; however, recent studies have demonstrated the significant impact of VL induction of these damaging species and the subsequent activation of inflammatory cytokines and matrix metalloproteinases.[50,61] In *ex vivo* skin explant studies, results demonstrate an estimated 50% generation of ROS attributed to VL exposure, compared to 4% attributed to UV-B and 46% to UV-A exposure.[62] Studies indicate that VL-mediated ROS and RNS generation can damage the skin barrier, leading to photoaging, hyperpigmentation, and melasma, especially in FSTs IV to VI.[11,63-67] ROS generation leads to bystander damage to healthy skin cells and the alteration of endogenous antioxidant levels important for preventing additional skin damage.[68,69] Further, in melanin-containing cells, VL-induced ROS and RNS can cause radiation-independent pyrimidine dimer formation.[6,31,51,70,71]

Though a high amount of free radical formation is mediated by UV radiation, studies have revealed that approximately 50% of free radicals are induced by VL and infrared radiation (IR), findings that were confirmed by *in vivo* studies showing the VL- and IR-induced degradation of cutaneous carotenoid antioxidants.[62,69,72,73] The excess generation of free-radical formation exceeding the free radical threshold value is detrimental to overall skin health, leading to DNA damage and melanogenesis.[62]

The cascade of events initiated by the induction of free radicals and reactive species results in the elevation of proinflammatory mediators and tissue destructive enzymes, including the matrix metalloproteinases, resulting in DNA and tissue damage associated with photoaging and melanogenesis.[61,74,75] More recently, the induction of free radicals has been identified to originate via activation of the Opsin-3 receptor.[39]

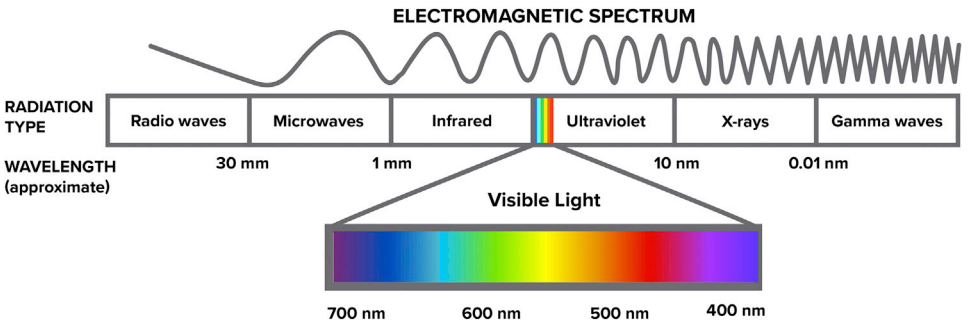

Fig 1. Electromagnetic spectrum.

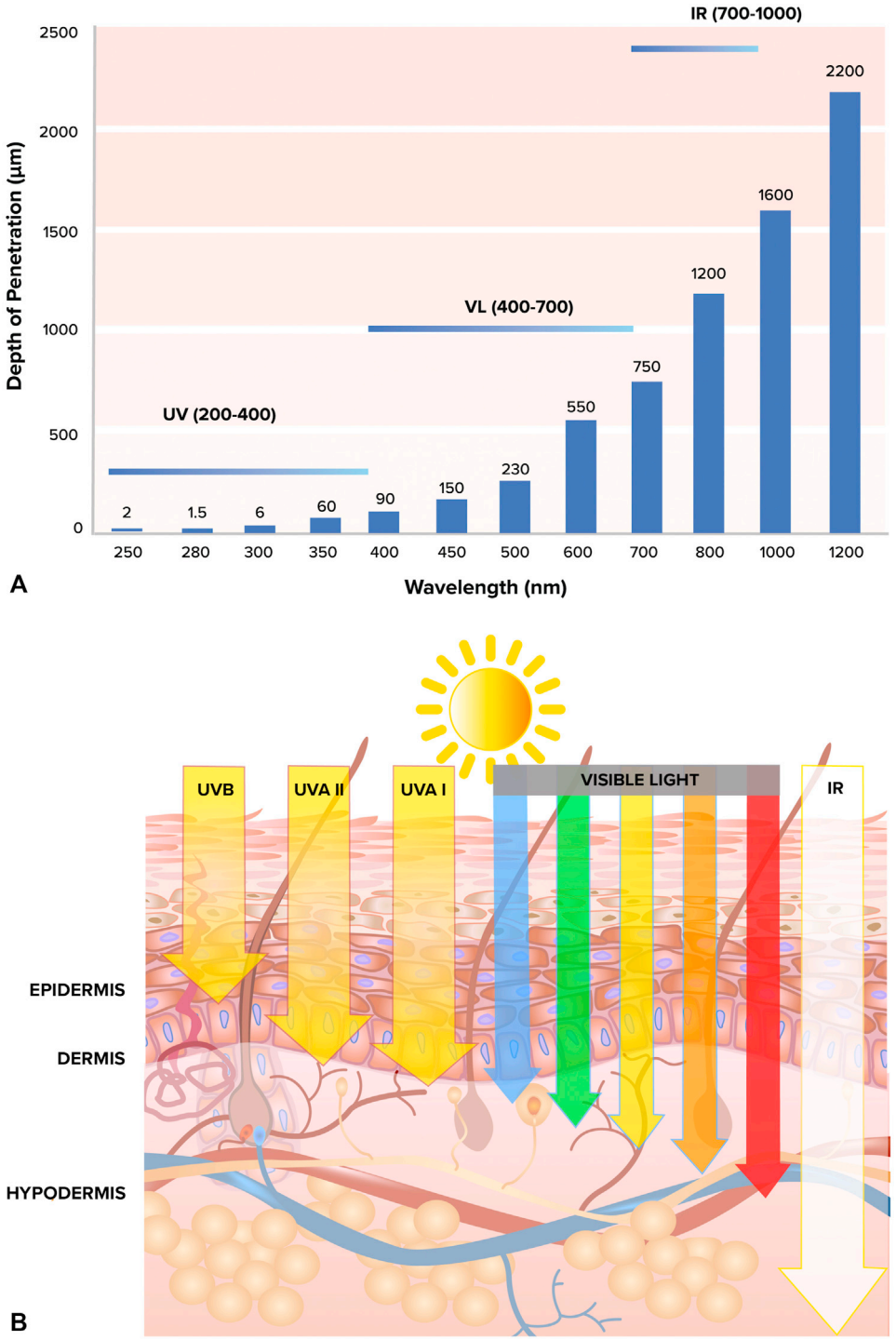

Fig 2. Visible light: depth of penetration.[16] **A**, Red light penetrates the full thickness of the epidermis and dermis, reaching the subcutaneous adipose layer, while blue light has less penetration, demonstrating the proportionality of the wavelength to the depth of penetration and inverse relationship to energy. **B**, Schematic of depth of penetration, all sunlight. *IR*, Infrared.

VL-induced melanogenesis is most pronounced in FSTs IV to VI,[12,14,52] with reports of both transient and long-lasting (up to 8 weeks) pigmentation in human skin, dependent upon the total dose.[59,76,77] It has been proposed that the production of immediate pigmentation after VL exposure is photochemical in nature, while delayed pigmentation results from neo-melanogenesis.[14] VL exposure in

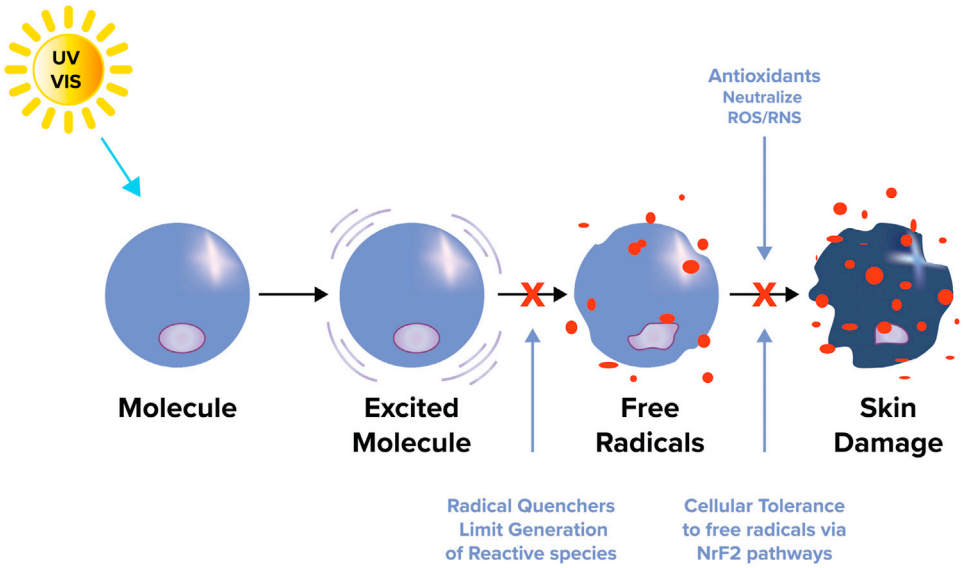

Fig 3. Role of radical quenchers and antioxidants in limiting UV/visible light-induced skin damage. Radical quenchers function by limiting the generation of reactive species, while antioxidants neutralize ROS and RNS. Antioxidant molecules, such as licochalcone A, function by enhancing cellular tolerance to free radicals via the Nrf2 pathway. *RNS*, Reactive nitrogen species; *ROS*, reactive oxygen species; *VIS*, visible light.

FSTs IV to VI leads to the activation of the OPN3 melanocyte sensor, initiating a cascade of reactions culminating in the increase of the melanogenesis enzymes tyrosinase and dopachrome tautomerase. Additionally, VL induces the formation of a protein complex between tyrosinase and dopachrome tautomerase instrumental for maintaining tyrosinase activity in FST III and higher, leading to hyperpigmentation.[14] The overall impact of VL on the induction of reactive species results in the activation of multiple pathways, culminating in DNA damage via ROS and RNS, hyperpigmentation, and melanogenesis induced by tyrosinase activity and photoaging, with the result of the stimulation of inflammatory mediators and destructive matrix metalloproteinases affecting both the appearance and the architecture of the skin barrier.

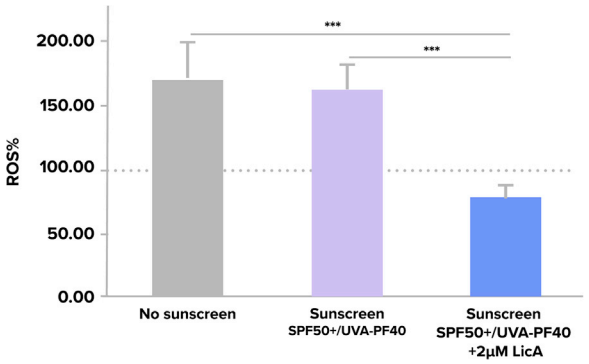

Fig 4. The effects of antioxidant licochalcone A on the reduction of ROS[79] are significant increase in reduction in percent ROS with the addition of licochalcone A to sunscreen. *LicA*, Licochalcone A; *PF*, protection factor; *ROS*, reactive oxygen species; *SPF*, sun protection factor.

ROLE OF ANTIOXIDANTS IN PREVENTING SKIN DAMAGE

Oxidative stress mediated by both UV and VL initiates multiple pathways affecting skin health, as previously described. Natural endogenous antioxidants have evolved to protect the skin from environmental stimuli and ensure skin rejuvenation and protection. These endogenous antioxidants and free radical scavengers include glutathione, uric acid, α-tocopherol, squalene, coenzyme Q_{10}, and others.[78] Unfortunately, this natural protective system is not unlimited when the skin is exposed to excessive UV and VL, and the breakdown of this system can occur, leading to a disruption of skin health, including DNA damage, hyperpigmentation, and melanogenesis.[4-7,11,12,14,15,49,50,58-60] One approach to providing additional photoprotection is via the use of supplemental antioxidants and radical quenchers to support or enhance the skin's endogenous system (Fig 3).

Several exogenous antioxidants and free radical scavengers have been identified, including vitamin E (α-tocopherol), vitamin C, licochalcone A, and diethylhexyl syringylidene malonate.[79,80] Vitamin E is a potent antioxidant that inhibits the production of

ROS molecules when lipids undergo oxidation and during the propagation of free radical reaction.[81,82] Due to vitamin E's peroxyl radical-scavenging activity, it can aid in the protection of phospholipids and fatty acids in the skin's membrane phospholipids,[83] and recent studies demonstrated vitamin E inhibition of UV-A–induced cyclobutene pyrimidine dimers and oxidatively generated DNA damage in keratinocytes.[84] Vitamin C (ascorbic acid) is usually present in high concentrations in the skin; however, several reports have demonstrated low levels of vitamin C in aged or photodamaged skin due to excessive exposure to oxidative stress stimulants, including pollutants and UV radiation.[85-88] Vitamin C's antioxidant activity is maximized when present in conjunction with vitamin E; when combined, they act to limit oxidative damage to cell membrane structures.[89-94]

Licochalcone A is a root extract of *Glycyrrhiza inflata* and has been identified as a potent antioxidant, inhibiting UV-induced ROS generation, and an activator of the Nrf transcription factor, a key player in the cellular stress response due to its regulation of cytoprotective genes.[79,95,96] Mann et al[79] recently demonstrated a decrease in VL- and UV-induced ROS formation to a level equivalent to unirradiated fibroblast cells, or even below, when irradiated with UV and VL. Licochalcone A also showed protective effects on cutaneous carotenoids *in vivo* (Fig 4). Taken together, the use of exogenous antioxidants and radical scavengers can supplement the endogenous antioxidant system of the skin, aiding in overall photoprotection.

INTELLIGENT DESIGN OF NEXT-GENERATION PHOTOPROTECTION AGAINST UV- AND VL-INDUCED SKIN DAMAGE

Given the increased awareness of the need for photoprotection, not only from UV-A and UV-B radiation but also from VL, it is imperative to work toward establishing novel approaches to the development of photoprotection options for patients with all FSTs. Currently, UV filters utilized in sunscreens are either organic (ie, chemical), or inorganic (ie, mineral) (Table I), with the primary focus on absorption in the UV-A/UV-B range.

Increases in the availability of photoprotection products that include VL protection are emerging and advancing, focused on either VL blocking (ie, tinted sunscreens) or the generation of reactive species and radical quenching (ie, antioxidant sunscreens). The inorganic or physical filters currently available center on the ability of naturally occurring minerals (ie, titanium dioxide, zinc oxide, and iron oxide) to reflect and scatter VL when the particle sizes are >200 nm[15,97,98]; however, the large-sized particles create a residual whitish appearance on the skin, making them noncosmetically attractive, especially in FSTs IV to VI.[97,98] Attempts to utilize micronized zinc and titanium particles have resulted in improved skin appearance but decreased VL-blocking capacity.[15,99,100] Early attempts to develop antioxidant-based VL sunscreens (ie, vitamin E cream) demonstrated no effects on VL-induced pigmentation,[101] while efforts of the use of antioxidant complexes showed less pigmentation immediately after VL irradiation compared to untreated sites but no statistically significant differences in pigmentation after 7 days.[13,60] More recently, Ezekwe et al[102] presented preliminary results demonstrating a significant decrease in clinical scores for hyperpigmentation at day 7 post-VL + UV-A1 irradiation using tinted organic sunscreen compared to an irradiated untreated control. Recent advances in the incorporation of antioxidants and radical scavengers using simple antioxidants blended into sunscreen formulations, thereby addressing the VL induction of ROS/RNS, have looked promising.

Lyons et al[103] showed that an antioxidant blend topically applied to the skin containing a variable concentration of a singlet oxygen quencher (diethylhexyl syringylidene malonate at 1% and 2%) and fixed concentrations of vitamin E (0.25%) and vitamin C (0.01%) can inhibit erythema in FST I to III and reduce pigmentation in FST IV to VI caused by VL + UV-A1. Ruvolo et al (unpublished data) demonstrated a significant reduction in VL-induced hyperpigmentation with sunscreen containing a vitamin E, vitamin C,

Table I. Approved UV filters in the 1999 US Food and Drug Administration Sunscreen Monograph[58]

Active ingredient	Absorption	Maximum concentration (%)
Avobenzone	UV-A	3
Cinoxate	UV-B	3
Dioxybenzone	UV-B, UV-A2	3
Ensulizole	UV-B	4
Homosalate	UV-B	15
Meradimate	UV-A2	5
Octinoxate	UV-B	7.5
Octisalate	UV-B	5
Octocrylene	UV-B, UV-A2	10
Oxybenzone	UV-B, UV-A2	6
Padimate O	UV-B	8
Sulisobenzone	UV-B, UV-A2	10
Titanium Dioxide	UV-B, UV-A2, UV-A1	25
Zinc Oxide	UV-B, UV-A2, UV-A1	25

Adapted from Geisler et al[58] with permission from the Journal American Academy of Dermatology, Elsevier.

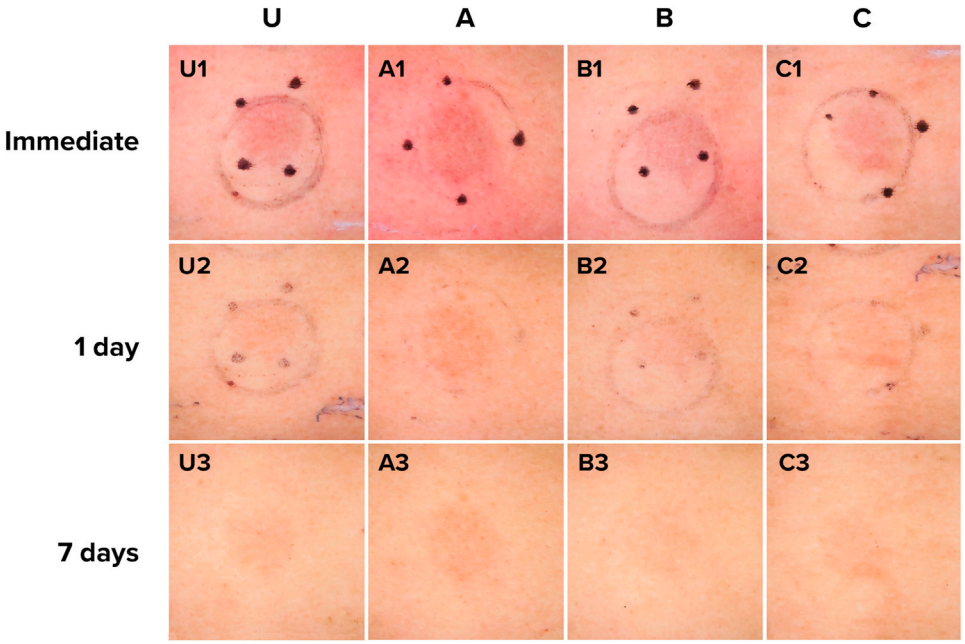

Fig 5. Effects of antioxidant-enriched sunscreen formulations. Cross-polarized images from sites exposed to 380 J/cm^2. *U*: Untreated control: *U1*, immediate; *U2*, 24 hours; and *U3*, 7 days after exposure. *A*: Sunscreen SPF 50, no antioxidants: *A1*, immediate; *A2*, 24 hours; and *A3*, 7 days after exposure. *B*: Tinted sunscreen, SPF 20 (10.66% titanium dioxide): *B1*, immediate; *B2*, 24 hours; and *B3*, 7 days after exposure. *C*: Sunscreen SPF 50 with 5 antioxidants (0.5% diethylhexyl syringylidene malonate, 0.25% vitamin E, 0.025% vitamin C, 0.025% licochalcone A, 0.01% glycyrrhetinic acid): *C1*, immediate; *C2*, 24 hours; and *C3*, 7 days after exposure. *SPF*, Sun protection factor.

diethylhexyl syringylidene malonate, licochalcone A, and glycyrrhetinic acid antioxidant mixture compared to that treated with sunscreen without antioxidants. The protection was equivalent to that offered by tinted sunscreen (Figs 5 and 6).

This nontinted formulation may aid in the overall compliance and adherence to use of photoprotective sunscreens, especially in patients most vulnerable to VL-induced pigmentation disorders, including those with FSTs IV to VI.

SUMMARY AND CONCLUSION

There is an increasing knowledge base on the impact of VL on skin health, including erythema, some photodermatoses, hyperpigmentation, and melasma, especially in individuals with FST IV-VI. Current photoprotection options for both UV and VL are limited to tinted sunscreens, which are often not cosmetically appealing and are, therefore, often not utilized. The development of new filters that cover the UV and VL ranges may help to fill this gap in protection. In addition, recent advances in understanding the role of VL's induction of reactive species has opened doors to the generation of antioxidant-based formulations, which have shown promise as novel alternatives for photoprotection for all skin types.

The authors thank Rene Alvarez, PhD, and Valerie Sanders from Evince Communications for providing editorial support, including development of the rough draft of the manuscript, based exclusively on the outline and input from the corresponding authors. This assistance was funded via unrestricted educational funding from Beiersdorf, Inc, which supported this work. The final version solely represents the views of the authors and was approved by each author prior to submission.

Conflicts of interest

Dr Lim has served as an investigator (grant to institution) for Incyte, L'Oréal, Pfizer, Patient-Centered Outcomes Research Institute (PCORI); as a consultant for Pierre Fabre, ISDIN, Ferndale, La Roche-Posay, Beiersdorf; and as a speaker in a general education session for La Roche-Posay and Cantabria Labs. Dr Kohli is an investigator for Ferndale, Estee Lauder, La Roche-Posay Dermatologique, Unigen, Johnson & Johnson, Allergan, and Bayer and has received support from the American Skin Association for a vitiligo project (grant to institution); has served as a consultant for Pfizer and Johnson and Johnson, with fee and equipment received by the institution, respectively; and has received honorarium as a consultant for Beiersdorf

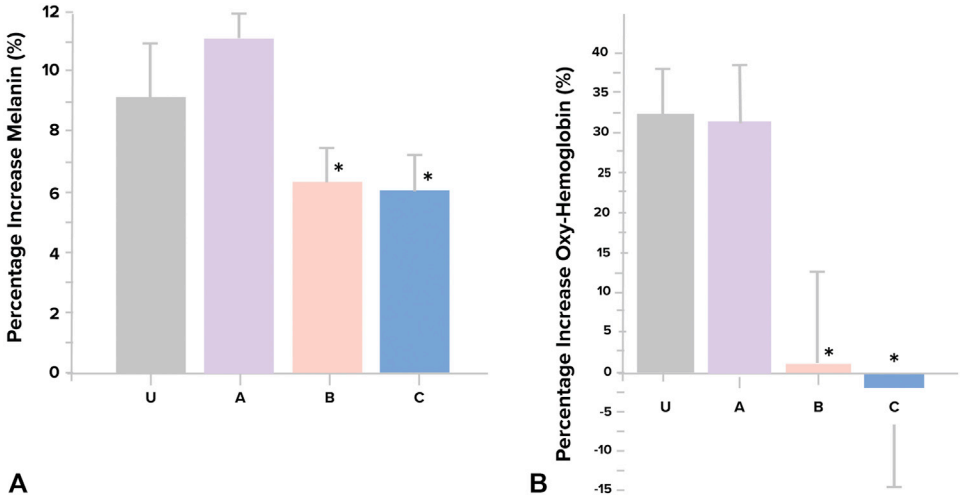

Fig 6. Effects of antioxidant-enriched sunscreen formulations on melanin and oxyhemoglobin. Percentage increase in (**A**) melanin and (**B**), oxyhemoglobin by diffuse reflectance spectroscopy. Data illustrate the average increase for the 3 time points in the study: immediate, 24 hours, and 7 days after the skin exposure to 380 J/cm^2. *U*, untreated control; *A*, sunscreen SPF 50, no antioxidants; *B*, tinted sunscreen, SPF 20 (10.66% titanium dioxide); and *C*, sunscreen SPF 50 with 5 antioxidants (0.5% diethylhexyl syringylidene malonate, 0.25% vitamin E, 0.025% vitamin C, 0.025% licochalcone A, 0.01% glycyrrhetinic acid). *SPF*, Sun protection factor.

and ISDIN. Mr Ruvolo and Dr Kolbe are employees of Beiersdorf, Inc. Dr Hamzavi has served as an investigator (grant to institution) for Pfizer Inc, Bayer, Lenicura, Incyte, Estee Lauder, L'Oréal, Unigen, Avita, Arcutis, and Ferndale Laboratories, Inc; as an Advisory Board member for AbbVie; as a Consultant to Galderma Laboratories, LP, Incyte, Pfizer, UCB, Boehringer Ingelheim, and Clarify Medical. Evince Communications has served as scientific consultants for Beiersdorf, Inc, on educational initiatives and the dermMentors Resident of Distinction Award Program.

REFERENCES

1. Yang MF, Tuchin VV, Yroslavsky AN. Principles of light-skin interactions. In: Baron E, ed. *Light-Based Therapies for Skin of Color*. Springer-Verlag; 2009:1-44.
2. Diffey BL. What is light? *Photodermatol Photoimmunol Photomed*. 2002;18:68-74.
3. Frederick JE, Snell HE, Haywood EK. Solar ultraviolet radiation at the earth's surface. *Photochem Photobiol*. 1989;50:443-450.
4. Kohli I, Braunberger TL, Nahhas AF, et al. Long-wavelength ultraviolet A1 and visible light photoprotection: a multimodality assessment of dose and response. *Photochem Photobiol*. 2020;96:208-214.
5. Kohli I, Chaowattanapanit S, Mohammad TF, et al. Synergistic effects of long-wavelength ultraviolet A1 and visible light on pigmentation and erythema. *Br J Dermatol*. 2018;178:1173-1180.
6. Austin E, Geisler AN, Nguyen J, et al. Visible light. Part I: properties and cutaneous effects of visible light. *J Am Acad Dermatol*. 2021;84:1219-1231.
7. Coats JG, Maktabi B, Abou-Dahech MS, Baki G. Blue light protection, part I-effects of blue light on the skin. *J Cosmet Dermatol*. 2021;20:714-717.
8. Coats JG, Maktabi B, Abou-Dahech MS, Baki G. Blue light protection, part II-ingredients and performance testing methods. *J Cosmet Dermatol*. 2021;20:718-723.
9. Duteil L, Queille-Roussel C, Lacour JP, Montaudié H, Passeron T. Short-term exposure to blue light emitted by electronic devices does not worsen melasma. *J Am Acad Dermatol*. 2020;83:913-914.
10. Ou-Yang H, Stamatas G, Kollias N. Spectral responses of melanin to ultraviolet A irradiation. *J Invest Dermatol*. 2004;122:492-496.
11. Dupont E, Gomez J, Bilodeau D. Beyond UV radiation: a skin under challenge. *Int J Cosmet Sci*. 2013;35:224-232.
12. Searle T, Al-Niaimi F, Ali FR. Visible light and hyperpigmentation: the invisible culprit. *Clin Exp Dermatol*. 2021;46(5):995-997.
13. Schalka S. New data on hyperpigmentation disorders. *J Eur Acad Dermatol Venereol*. 2017;31:18-21.
14. Randhawa M, Seo I, Liebel F, Southall MD, Kollias N, Ruvolo E. Visible light induces melanogenesis in human skin through a photoadaptive response. *PLoS One*. 2015;10:e0130949.
15. Cohen L, Brodsky MA, Zubair R, Kohli I, Hamzavi IH, Sadeghpour M. Cutaneous interaction with visible light: what do we know. *J Am Acad Dermatol*. Published online April 11, 2020. https://doi.org/10.1016/j.jaad.2020.03.115
16. Anderson RR, Parrish JA. The optics of human skin. *J Invest Dermatol*. 1981;77:13-19.
17. Wang EB, Kaur R, Fierro M, Austin E, Jones LR, Jagdeo J. Safety and penetration of light into the brain. In: Hamblin MR, Huang Y-Y, eds. *Photobiomodulation in the Brain: Low-Level Laser (Light) Therapy in Neurology and Neuroscience*. Elsevier; 2019:49-66.
18. Jacques SL. Optical properties of biological tissues: a review. *Phys Med Biol*. 2013;58:R37-R61.
19. Hu D, van Zeyl M, Valter K, Potas JR. Sex, but not skin tone affects penetration of red-light (660 nm) through sites susceptible to sports injury in lean live and cadaveric tissues. *J Biophotonics*. 2019;12:e201900010.

20. Salehpour F, Cassano P, Rouhi N, et al. Penetration profiles of visible and near-infrared lasers and light-emitting diode light through the head tissues in animal and human species: a review of literature. *Photobiomodul Photomed Laser Surg*. 2019;37:581-595.
21. Clement M, Daniel G, Trelles M. Optimising the design of a broad-band light source for the treatment of skin. *J Cosmet Laser Ther*. 2005;7:177-189.
22. Kocsis L, Herman P, Eke A. The modified Beer-Lambert law revisited. *Phys Med Biol*. 2006;51:N91-N98.
23. Planck M. On the law of the energy distribution in the normal spectrum. *Ann Phys*. 1901;4:1-11.
24. Okuno T, Saito H, Ojima J. Evaluation of blue-light hazards from various light sources. *Dev Ophthalmol*. 2002;35:104-112.
25. Lister T, Wright PA, Chappell PH. Optical properties of human skin. *J Biomed Opt*. 2012;17:90901.
26. Nielsen KP, Zhao L, Stamnes JJ, Stamnes K, Moan J. The optics of human skin: aspects important for human health. In: Bjertness E, ed. *Solar Radiation and Human Health. The Norwegian Academy of Science and Letters*. 2008:35-46.
27. Hunt G, Kyne S, Ito S, Wakamatsu K, Todd C, Thody A. Eumelanin and phaeomelanin contents of human epidermis and cultured melanocytes. *Pigment Cell Res*. 1995;8:202-208.
28. Micillo R, Panzella L, Koike K, Monfrecola G, Napolitano A, d'Ischia M. "Fifty shades" of black and red or how carboxyl groups fine tune eumelanin and pheomelanin properties. *Int J Mol Sci*. 2016;17(5):746.
29. Vincensi MR, d'Ischia M, Napolitano A, et al. Phaeomelanin versus eumelanin as a chemical indicator of ultraviolet sensitivity in fair-skinned subjects at high risk for melanoma: a pilot study. *Melanoma Res*. 1998;8:53-58.
30. Zonios G, Dimou A, Bassukas I, Galaris D, Tsolakidis A, Kaxiras E. Melanin absorption spectroscopy: new method for noninvasive skin investigation and melanoma detection. *J Biomed Opt*. 2008;13:014017.
31. Brenner M, Hearing VJ. The protective role of melanin against UV damage in human skin. *Photochem Photobiol*. 2008;84:539-549.
32. McGrath JA, Eady RAJ, Pope FM. Anatomy and organization of human skin. In: Burns T, ed. *Rook's Textbook of Dermatology*. 7th ed. Blackwell Science Ltd; 2004:45-128.
33. Saidi IS, Jacques SL, Tittel FK. Mie and Rayleigh modeling of visible-light scattering in neonatal skin. *Appl Opt*. 1995;34:7410-7418.
34. Graaff R, Aarnoudse JG, Zijp JR, et al. Reduced light-scattering properties for mixtures of spherical particles: a simple approximation derived from Mie calculations. *Appl Opt*. 1992;31:1370-1376.
35. Berg JM, Tymoczko JL, Stryer L. Hemoglobin: portrait of a protein in action. In: *Biochemistry*. 7th ed. Palgrave Macmillan; 2011:195-218.
36. Suh S, Choi EH, Atanaskova Mesinkovska N. The expression of opsins in the human skin and its implications for photobiomodulation: a systematic review. *Photodermatol Photoimmunol Photomed*. 2020;36:329-338.
37. Terakita A. The opsins. *Genome Biol*. 2005;6:213.
38. Olinski LE, Lin EM, Oancea E. Illuminating insights into opsin 3 function in the skin. *Adv Biol Regul*. 2020;75:100668.
39. Setty SR. Opsin3-a link to visible light-induced skin pigmentation. *J Invest Dermatol*. 2018;138:13-15.
40. Castellano-Pellicena I, Uzunbajakava NE, Mignon C, Raafs B, Botchkarev VA, Thornton MJ. Does blue light restore human epidermal barrier function via activation of Opsin during cutaneous wound healing? *Lasers Surg Med*. 2019;51:370-382.
41. Tsutsumi M, Ikeyama K, Denda S, et al. Expressions of rod and cone photoreceptor-like proteins in human epidermis. *Exp Dermatol*. 2009;18:567-570.
42. Lamb TD, Collin SP, Pugh EN Jr. Evolution of the vertebrate eye: opsins, photoreceptors, retina and eye cup. *Nat Rev Neurosci*. 2007;8:960-976.
43. Haltaufderhyde K, Ozdeslik RN, Wicks NL, Najera JA, Oancea E. Opsin expression in human epidermal skin. *Photochem Photobiol*. 2015;91:117-123.
44. Darvin ME, Sterry W, Lademann J, Vergou T. The role of carotenoids in human skin. *Molecules*. 2011;16:10491-10506.
45. Stahl W, Sies H. Bioactivity and protective effects of natural carotenoids. *Biochim Biophys Acta*. 2005;1740:101-107.
46. Darvin ME, Gersonde I, Meinke MC, Sterry W, Lademann J. Non-invasive in vivo determination of the carotenoids beta-carotene and lycopene concentrations in the human skin using the Raman spectroscopic method. *J Phys D Appl Phys*. 2005;38:2696-2700.
47. Terao J, Minami Y, Bando N. Singlet molecular oxygen-quenching activity of carotenoids: relevance to protection of the skin from photoaging. *J Clin Biochem Nutr*. 2011;48:57-62.
48. Krinsky NI, Yeum KJ. Carotenoid-radical interactions. *Biochem Biophys Res Commun*. 2003;305:754-760.
49. Kohli I, Zubair R, Lyons AB, et al. Impact of Long-wavelength ultraviolet A1 and visible light on light-skinned individuals. *Photochem Photobiol*. 2019;95:1285-1287.
50. Mahmoud BH, Hexsel CL, Hamzavi IH, Lim HW. Effects of visible light on the skin. *Photochem Photobiol*. 2008;84:450-462.
51. Jagdeo J, Nguyen JK, Ho D, et al. Safety of light emitting diode-red light on human skin: two randomized controlled trials. *J Biophotonics*. 2020;13:e201960014.
52. Fatima S, Braunberger T, Mohammad TF, Kohli I, Hamzavi IH. The role of sunscreen in melasma and postinflammatory hyperpigmentation. *Indian J Dermatol*. 2020;65:5-10.
53. Callender VD, St Surin-Lord S, Davis EC, Maclin M. Post-inflammatory hyperpigmentation: etiologic and therapeutic considerations. *Am J Clin Dermatol*. 2011;12:87-99.
54. Davis EC, Callender VD. Postinflammatory hyperpigmentation: a review of the epidemiology, clinical features, and treatment options in skin of color. *J Clin Aesthet Dermatol*. 2010;3:20-31.
55. Verallo-Rowell VM, Pua JM, Bautista D. Visible light photopatch testing of common photocontactants in female Filipino adults with and without melasma: a cross-sectional study. *J Drugs Dermatol*. 2008;7:149-156.
56. Kohli I, Lim HW, Hamzavi IH. Caution regarding testing for long wavelength ultraviolet A1 and visible light effects on human skin in vivo. *Photodermatol Photoimmunol Photomed*. 2020;36:58-60.
57. Boonstra HE, van Weelden H, Toonstra J, van Vloten WA. Polymorphous light eruption: a clinical, photobiologic, and follow-up study of 110 patients. *J Am Acad Dermatol*. 2000;42:199-207.
58. Geisler AN, Austin E, Nguyen J, Hamzavi I, Jagdeo J, Lim HW. Visible light. Part II: photoprotection against visible and ultraviolet light. *J Am Acad Dermatol*. 2021;84:1233-1244.
59. Mahmoud BH, Ruvolo E, Hexsel CL, et al. Impact of long-wavelength UVA and visible light on melanocompetent skin. *J Invest Dermatol*. 2010;130:2092-2097.
60. Zubair R, Kohli I, Lyons AB. Mitigating visible light-induced pigmentation with topical antioxidants. Presented at: 15th Annual Skin of Color. *Scientific Symposium*. 2019.
61. Liebel F, Kaur S, Ruvolo E, Kollias N, Southall MD. Irradiation of skin with visible light induces reactive oxygen species and

matrix-degrading enzymes. *J Invest Dermatol*. 2012;132:1901-1907.
62. Zastrow L, Lademann J. Light-instead of UV protection: new requirements for skin cancer prevention. *Anticancer Res*. 2016;36:1389-1393.
63. Nakashima Y, Ohta S, Wolf AM. Blue light-induced oxidative stress in live skin. *Free Radic Biol Med*. 2017;108:300-310.
64. Cordeiro RM. Reactive oxygen species at phospholipid bilayers: distribution, mobility and permeation. *Biochim Biophys Acta*. 2014;1838:438-444.
65. Godley BF, Shamsi FA, Liang FQ, Jarrett SG, Davies S, Boulton M. Blue light induces mitochondrial DNA damage and free radical production in epithelial cells. *J Biol Chem*. 2005;280:21061-21066.
66. Passeron T. Melasma pathogenesis and influencing factors - an overview of the latest research. *J Eur Acad Dermatol Venereol*. 2013;27(S1):5-6.
67. Passeron T, Picardo M. Melasma, a photoaging disorder. *Pigment Cell Melanoma Res*. 2018;31:461-465.
68. Liang D. A salutary role of reactive oxygen species in intercellular tunnel-mediated communication. *Front Cell Dev Biol*. 2018;6:2.
69. Vandersee S, Beyer M, Lademann J, Darvin ME. Blue-violet light irradiation dose dependently decreases carotenoids in human skin, which indicates the generation of free radicals. *Oxid Med Cell Longev*. 2015;2015:579675.
70. Cope FW, Sever RJ, Polis BD. Reversible free radical generation in the melanin granules of the eye by visible light. *Arch Biochem Biophys*. 1963;100(2):171-177.
71. Chiarelli-Neto O, Ferreira AS, Martins WK, et al. Melanin photosensitization and the effect of visible light on epithelial cells. *PLoS One*. 2014;9:e113266.
72. Darvin ME, Haag S, Meinke M, Zastrow L, Sterry W, Lademann J. Radical production by infrared A irradiation in human tissue. *Skin Pharmacol Physiol*. 2010;23:40-46.
73. Darvin ME, Haag SF, Lademann J, Zastrow L, Sterry W, Meinke MC. Formation of free radicals in human skin during irradiation with infrared light. *J Invest Dermatol*. 2010;130:629-631.
74. Huang AH, Chien AL. Photoaging: a review of current literature. *Curr Dermatol Rep*. 2020;9:22-29.
75. McDaniel D, Farris P, Valacchi G. Atmospheric skin aging-contributors and inhibitors. *J Cosmet Dermatol*. 2018;17:124-137.
76. Pathak MA, Riley FC, Fitzpatrick TB. Melanogenesis in human skin following exposure to long-wave ultraviolet and visible light. *J Invest Dermatol*. 1962;39:435-443.
77. Kollias N, Baqer A. An experimental study of the changes in pigmentation in human skin in vivo with visible and near infrared light. *Photochem Photobiol*. 1984;39:651-659.
78. Steenvoorden DP, van Henegouwen GM. The use of endogenous antioxidants to improve photoprotection. *J Photochem Photobiol B*. 1997;41:1-10.
79. Mann T, Eggers K, Rippke F, et al. High-energy visible light at ambient doses and intensities induces oxidative stress of skin-protective effects of the antioxidant and Nrf2 inducer licochalcone A in vitro and in vivo. *Photodermatol Photoimmunol Photomed*. 2020;36:135-144.
80. Nahhas AF, Abdel-Malek ZA, Kohli I, Braunberger TL, Lim HW, Hamzavi IH. The potential role of antioxidants in mitigating skin hyperpigmentation resulting from ultraviolet and visible light-induced oxidative stress. *Photodermatol Photoimmunol Photomed*. 2019;35:420-428.
81. Rizvi S, Raza ST, Ahmed F, Ahmad A, Abbas S, Mahdi F. The role of vitamin E in human health and some diseases. *Sultan Qaboos Univ Med J*. 2014;14:e157-e165.
82. Burton GW, Joyce A, Ingold KU. Is vitamin E the only lipid-soluble, chain-breaking antioxidant in human blood plasma and erythrocyte membranes? *Arch Bioichem Biophys*. 1983;221:281-290.
83. Tran K, Wong JT, Lee E, Chan AC, Choy PC. Vitamin E potentiates arachidonate release and phospholipase A2 activity in rat heart myoblastic cells. *Biochem J*. 1996;319(Pt2):385-391.
84. Delinasios GJ, Karbaschi M, Cooke MS, Young AR. Vitamin E inhibits the UVAI induction of "light" and "dark" cyclobutane pyrimidine dimers, and oxidatively generated DNA damage, in keratinocytes. *Sci Rep*. 2018;8:423.
85. Pullar JM, Carr AC, Vissers MCM. The roles of vitamin C in skin health. *Nutrients*. 2017;9(8):866.
86. Rhie G, Shin MH, Seo JY, et al. Aging- and photoaging-dependent changes of enzymic and nonenzymic antioxidants in the epidermis and dermis of human skin in vivo. *J Invest Dermatol*. 2001;117:1212-1217.
87. Shindo Y, Witt E, Han D, Epstein W, Packer L. Enzymic and non-enzymic antioxidants in epidermis and dermis of human skin. *J Invest Dermatol*. 1994;102:122-124.
88. McArdle F, Rhodes LE, Parslew R, Jack CI, Friedmann PS, Jackson MJ. UVR-induced oxidative stress in human skin in vivo: effects of oral vitamin C supplementation. *Free Radic Biol Med*. 2002;33:1355-1362.
89. Stewart MS, Cameron GS, Pence BC. Antioxidant nutrients protect against UVB-induced oxidative damage to DNA of mouse keratinocytes in culture. *J Invest Dermatol*. 1996;106:1086-1089.
90. Lin JY, Selim MA, Shea CR, et al. UV photoprotection by combination topical antioxidants vitamin C and vitamin E. *J Am Acad Dermatol*. 2003;48:866-874.
91. Darr D, Dunston S, Faust H, Pinnell S. Effectiveness of antioxidants (vitamin C and E) with and without sunscreens as topical photoprotectants. *Acta Derm Venereol*. 1996;76:264-268.
92. Dreher F, Gabard B, Schwindt DA, Maibach HI. Topical melatonin in combination with vitamins E and C protects skin from ultraviolet-induced erythema: a human study in vivo. *Br J Dermatol*. 1998;139:332-339.
93. Mukai K, Nishimura M, Ishizu K, Kitamura Y. Kinetic study of the reaction of vitamin C with vitamin E radicals (tocopheroxyls) in solution. *Biochim Biophys Acta*. 1989;991:276-279.
94. Tanaka K, Hashimoto T, Tokumaru S, Iguchi H, Kojo S. Interactions between vitamin C and vitamin E are observed in tissues of inherently scorbutic rats. *J Nutr*. 1997;127:2060-2064.
95. Kolbe L, Immeyer J, Batzer J, et al. Anti-inflammatory efficacy of Licochalcone A: correlation of clinical potency and in vitro effects. *Arch Dermatol Res*. 2006;298:23-30.
96. Kuhnl J, Roggenkamp D, Gehrke SA, et al. Licochalcone A activates Nrf2 in vitro and contributes to licorice extract-induced lowered cutaneous oxidative stress in vivo. *Exp Dermatol*. 2015;24:42-47.
97. Pinnell SR, Fairhurst D, Gillies R, Mitchnick MA, Kollias N. Microfine zinc oxide is a superior sunscreen ingredient to microfine titanium dioxide. *Dermatol Surg*. 2000;26:309-314.
98. Anderson MW, Hewitt JP, Spruce SR. Broad-spectrum physical sunscreens: titanium dioxide and zinc oxide. In: Lowe NJ, Shaath NA, Pathak MA, eds. *Sunscreens: Development,*

Evaluation and Regulatory Aspects. 1st. New York: Dekker; 1997:353-397.

99. Cole C, Shyr T, Ou-Yang H. Metal oxide sunscreens protect skin by absorption, not by reflection or scattering. *Photodermatol Photoimmunol Photomed*. 2016;32:5-10.
100. Bissonnette R, Nigen S, Bolduc C, Méry S, Nocera T. Protection afforded by sunscreens containing inorganic sunscreening agents against blue light sensitivity induced by aminolevulinic acid. *Dermatol Surg*. 2008;34:1469-1476.
101. Hexsel CL, Bangert SD, Hebert AA, Lim HW. Current sunscreen issues: 2007 Food and Drug Administration sunscreen labelling recommendations and combination sunscreen/insect repellent products. *J Am Acad Dermatol*. 2008;59:316-323.
102. Ezekewe N. Efficacy evaluation of topical sunscreens against long wavelength ultraviolet A1 and visible light induced biological effects: preliminary findings. Presented at: The 30th Annual Meeting of the Photodermatology Society; March 18, 2021; Virtual.
103. Lyons AB, Zubair R, Kohli I, et al. Mitigating visible light and long wavelength UVA1-induced effects with topical antioxidants. *Photochem Photobiol*. Published online September 22, 2021. https://doi.org/10.1111/php.13525