9-29-2021

Effects of visible light on mechanisms of skin photoaging

Aunna Pourang
Aaron Tisack
Nneamaka Ezekwe
Angeli E. Torres
Indermeet Kohli

See next page for additional authors
Authors
Aunna Pourang, Aaron Tisack, Nneamaka Ezekwe, Angeli E. Torres, Indermeet Kohli, Iltefat H. Hamzavi, and Henry W. Lim
Effects of visible light on mechanisms of skin photoaging

Aunna Pourang1 | Aaron Tisack2 | Nneamaka Ezekwe1 | Angeli E. Torres1 | Indermeet Kohli1,3 | Iltefat H. Hamzavi1 | Henry W. Lim1

1Photomedicine and Photobiology Unit, Department of Dermatology, Henry Ford Health System, Detroit, Michigan, USA
2Wayne State University School of Medicine, Detroit, Michigan, USA
3Department of Physics and Astronomy, Wayne State University, Detroit, Michigan, USA

Correspondence
Henry W. Lim, Department of Dermatology, Henry Ford Health System; 3031 W. Grand Blvd, Detroit, MI 48202, USA.
Email: hlim1@hfhs.org

Abstract
Human skin is not only affected by ultraviolet radiation but also by visible light wavelengths emitted by sunlight, electronic devices, and light emitting diodes. Similar to the ultraviolet radiation, visible light has been implicated in photoaging. In this review, the effects of blue light, yellow light, red light, and broad visible light are discussed in relation with photoaging. Different visible light wavelengths likely contribute beneficial and deleterious effects on photoaging by way of interaction with specific photoreceptors, ROS production, and other photon-mediated reactions. Further in vivo studies are needed to determine the mechanism and action spectrum of photoaging in humans, as well as optimal photoprotection with coverage against visible light wavelengths.

KEYWORDS
blue light, photoaging, red light, visible light, yellow light

1 | INTRODUCTION

Radiation emitted by sunlight that reaches the surface of the earth consists of ultraviolet A (UVA) (320-400 nm), ultraviolet B (UVB) (290-320 nm), visible (400-700 nm), and infrared (IR) (>700 nm) spectrums.1 Although most of the effects of photoaging on the skin have been studied in UV radiation (UVR), there has been increased interest in the effects of visible light (VL) on the skin. Humans are exposed to VL wavelengths through sunlight, light emitting diodes (LEDs) and electronic devices in the modern age, although the energy and fluence rate of the latter are not enough to cause skin damage.2 VL has been previously implicated to contribute to the photoaging seen in Fitzpatrick skin types I-III.3,4 Clinical manifestations of VL exposure, such as pigmentation, have been demonstrated in Fitzpatrick skin types IV-VI.5

Photoaging consists of rhytids decreased skin elasticity, lentigines, and mottled pigmentation. A major change associated with photoaging is breakdown of collagen and elastin.2 This process occurs as a result of inflammation resulting from UV-induced DNA damage and reactive oxidative species (ROS) generation, which lead to matrix metalloproteinase (MMP) formation in the epidermis and dermis and subsequent alterations of the extracellular matrix (ECM) components.6-9

While the mechanisms involved in UVR-induced photoaging have thoroughly been explored, further research is needed to understand if such mechanisms could be induced by VL, which in turn, requiring photoprotective measures to combat them.10 Additionally, this relatively new area of research is limited by a wide variety of wavelengths and irradiation protocols used among studies, which often do not accurately simulate natural exposure to sunlight or electronic devices.11,12 In this comprehensive review, we discuss the effects of various wavelengths of VL on photoaging of the skin.

1.1 | Broad visible light

1.1.1 | In vitro studies

In a study of human fibroblasts, ROS formed in a dose-dependent fashion following exposure to VL at doses equivalent to an hour of sunlight exposure during the summer (150 J/cm²). The rate of ROS generation was highest between wavelengths 400-450 nm, and
decreased continuously thereafter, with only minimal effects observed at wavelengths greater than 500 nm. This is consistent with the results observed from cultured human keratinocytes, which demonstrated a linear relationship between 405-nm VL dose and ROS formation, with a tendency to plateau at higher VL doses (>75 J/cm²). A quantitative analysis in another study showed that ROS formation increased by 5-, 9-, and 18-fold following exposure of skin equivalents to VL doses of 65, 130, and 180 J/cm², respectively. On the other hand, ROS formation is also thought to contribute to VL-induced photorejuvenation through collagen destruction, which can subsequently elicit new collagen formation. This was observed following exposure to broad VL (400-800 nm) at doses typically used for skin rejuvenation (20-40 J/cm²).

Another mechanism by which VL may induce photaging is through alterations in human fibroblast morphology and extracellular matrix (ECM) components. In an in vitro experiment by Zamarron et al., signs of cellular stress such as cytoplasmic retraction, long cytoplasmic projections, and cellular stretching were observed immediately and up to 48 hours after irradiation with VL at a dose of 247.3 J/cm². Significantly increased expression of collagenolytic enzymes, MMP-1 and cathepsin K (CTSK), was observed at 24 hours post-irradiation with the same dose. Interestingly, VL-irradiated fibroblasts showed increased expression of fibrillin 1, fibrillin 2, and elastin, which are otherwise decreased with chronologic aging.

When VL is combined with UVR and IR a synergistic effect is produced. This was shown in an in vitro study by Hudson et al where dermal fibroblasts exposed to complete solar radiation (UV +VL + IR at 108, 216, 432, and 756 J/m²) had significantly increased ROS generation, mitochondrial DNA damage, and nuclear DNA damage compared to each wavelength individually. In contrast, in a study using LED as a light source, the combined effects of VL (around 590 nm) and IR (around 870 nm) yielded an increase in collagen 1 and decrease in MMP-1 in one in-vitro study, suggesting an anti-aging effect. Of note, this effect was elicited at a fluence of 0.1 J/cm² with a fixed irradiance of 4.0 mW/cm²; the greatest effect was seen at a VL/IR ratio of 75%/25.

Different VL wavelengths also act through different photoreceptors in cells. Fibroblasts contain photoacceptors or chromophores that absorb light wavelengths with peaks at 420, 445, 470, 560, 630, 690, and 730 nm, with a general decrease in absorption at longer wavelengths. This may explain why longer wavelengths are not as deleterious in inducing photaging changes. Blue light has also been found to work through flavins and opsins in cells, while UVA and red light have been found to not work through opsins. Instead, low-intensity red light has been found to act on cells through the photoacceptor cytochrome C oxidase, the terminal enzyme of the mitochondrial electron transport chain.

### 1.1.2 Ex vivo and clinical studies

Human studies that explore the effects of VL on photaging are currently limited. One ex vivo study noted free radical formation following exposure to artificial solar light, with the VL component accounting for 33%. An irradiance-dependent increase in radical formation was demonstrated between 0.9-2.9 mW/cm². Cho et al exposed 16 healthy human volunteers to solar VL and IR equivalent to 1.1-3 of minimal erythema dose (MED) (average 163 ± 22.5 minutes of natural sunlight). Skin samples taken 24 hours post-irradiation showed increased expression of collagenolytic enzymes MMP-1 and MMP-9, and decreased expression of type 1 procollagen.

Alternatively, the combination of VL (405-425nm, 50mW/cm² to a dose of 45-60 J/cm²) and IR (850-890nm, 50mW/cm² to a dose of 45-60 J/cm²) has been used in the realm of esthetic dermatology practice for photorejuvenation, skin resurfacing, and smoothing of fine wrinkles. Taken together, the aforementioned studies demonstrate that depending on the parameters, VL can induce both pro- and anti-aging effects.

The addition of UVA to VL also has notable effects on the skin when compared to VL alone. Kohli et al irradiated ten subjects with Fitzpatrick skin phototype IV-VI with both VL containing less than 0.5% UVA1 and pure VL (80-480 J/cm²). Immediately after irradiation, erythema was noted only at the VL+UVA1 sites at 320-480 J/cm². Similarly, hyperpigmentation, assessed clinically, was noted at the VL+UVA1 site irradiated at both 320 J/cm² and 480 J/cm², which lasted through the 14 day follow-up. Pigmentation, assessed objectively by diffuse reflectance spectroscopy (DRS), was also noted to be higher at the VL+UVA1 sites when compared to the pure VL sites. Biopsies obtained from non-irradiated sites and those from sites irradiated with VL+UVA1 and pure VL at 480 J/cm². While melanoma antigen recognized by T cells (MART)-1, a marker for melanocytes, was not notably different among non-irradiated sites, irradiated sites, or between the 2 irradiated sites, there was a statistically significant increase in markers of both inflammation and cell proliferation cyclooxygenase-2 (COX-2) and cyclin D-1, respectively) in both VL+UVA1 and pure VL sites compared to unirradiated control. COX-2 and cyclin D-1 levels did not, however, differ between VL+UVA1 and pure VL sites. These results highlight the importance of photoprotection beyond UV wavelengths.

### 1.2 Blue Light (400-500 nm)

#### 1.2.1 In vitro studies

The effects of blue light (BL) wavelengths on photaging are similar to those induced by broad VL and UVR. Avola et al irradiated human epidermal keratinocytes and human dermal fibroblasts with LED-BL (450 nm) at various doses (5-45 J/cm²) and found that keratinocytes exposed to 45 J/cm² and fibroblasts exposed to 15 J/cm² demonstrated a reduction in cell viability, increased matrix metalloproteinase (MMP)-1 mRNA, decreased collagen type I mRNA and increased ROS. Keratinocytes were also noted to have decreased MMP-12 mRNA, and elastase. Similarly, fibroblasts exposed to various fluences of LED-BL (415 nm; 5-80 J/cm²) on fibroblasts demonstrated dose-dependent increases in ROS, and...
significant decreases in cell proliferation and fibroblast migration speed.\textsuperscript{28,29} Cell viability was not significantly altered by BL irradiation, which may have clinical implications in treating keloids and other fibrotic skin diseases.\textsuperscript{29}

Lorrio et al exposed human dermal fibroblasts and melanocytes to narrow-band LED lamp (450-465 nm; 38 and 76 J/cm\textsuperscript{2}), equivalent to spending 290 hours or 6 hours a day for 7 weeks in front of digital devices. Decreased cell viability was noted with increasing blue light doses (38 and 76 J/cm\textsuperscript{2}), with a more pronounced effect on melanocytes. Alterations of mitochondrial morphology and membrane potential, indicative of photoaging, as well as p38 melanogenic modulation, were noted in BL-irradiated (38 J/cm\textsuperscript{2}) fibroblasts as well. Three hours after BL irradiation, a significant darkening of extracellular and intracellular melanin pigments was noted in melanocytes after irradiation at a dose of 38 J/cm\textsuperscript{2}; the authors noted this change was likely a result of melanin photodestruction.\textsuperscript{11} Of note, the possibility of dose reciprocity failures and the potential for repair mechanisms must be considered, so that in-vitro cellular damage is not directly extrapolated to in vivo skin damage following exposure to digital devices.

Human dermal fibroblasts irradiated with BL (410 ± 10 nm and 480 ± 8 nm), as well as red (630 ± 8 nm) and yellow (595 ± 2 nm) wavelengths via LED module at various doses (1-40 J/cm\textsuperscript{2}) demonstrated decreased cell viability in the blue wavelengths but not red or yellow wavelengths.\textsuperscript{30}

\subsection*{1.2.2 Clinical studies}

Nakashima et al found that BL exposure of mouse skin in vivo produced oxidative stress preferentially in the skin mitochondria but did not observe this with green, red, far red or infrared light. In human keratinocytes, the efficiency with that BL produced oxidative stress was 25% that of UVA in human keratinocyte mitochondria, and 68% of UVA in mouse skin. Blue light reduced mouse and human skin flavin autofluorescence, suggesting that the formation of ROS likely occurred via flavins acting as the photosensitizer.\textsuperscript{12}

Vandersee et al exposed 9 healthy volunteers with Fitzpatrick skin types II and III to increasing doses of blue-violet light (380-495 nm, peak 440 nm; 50 J/cm\textsuperscript{2} and 100 J/cm\textsuperscript{2}) and assessed the effects of ROS and free radical formation indirectly via carotenoid concentration, an antioxidant naturally found in the human skin. There was a significant, inverse decrease in the carotenoid concentration in a dose-dependent manner, indicating the adverse effect of BL at higher doses.\textsuperscript{31}

In a clinical study by Campiche et al, the inner forearms of 33 female participants with skin phototypes III and IV were irradiated with a repetitive blue light (450 nm, 4 × 60 J/cm\textsuperscript{2}) over a 4 day period. Immediately after BL irradiation on day 3, oxygen saturation and hemoglobin measurements were significantly increased and resolved to pre-irradiation values 24 hours later. Melanin chromophore levels increased significantly at day 4 and remained constant until day 28. Skin color changes noted by chromameter measurements, expressed by a significant decrease in individual tyloptage angle (ITA\textsuperscript{A}) value, was also noted on day 3.\textsuperscript{32}

Another study compared BL (415 nm; 10-150 J/cm\textsuperscript{2}; Average Minimal Pigmentation Dose 58 ± 20 J/cm\textsuperscript{2}), red light (630 nm; Average Minimal Pigmentation Dose 10-150 J/cm\textsuperscript{2}, 150 ± 0 J/cm\textsuperscript{2}) and UVA (Average Minimal Pigmentation Dose 113 ± 42 mJ/cm\textsuperscript{2}) irradiation of healthy subjects with Fitzpatrick skin types III and IV.\textsuperscript{33} Immediate pigment darkening (IPD), accompanied by weak-to-moderate erythema, was observed 1 hour after BL exposure with the erythema disappearing after 24-48 hours. Hyperpigmentation, which was higher in skin type IV than skin type III, was noted through the end of the study (Day 22) and at a 3 month follow up visit. UVB-irradiated skin was also associated with increased pigmentation, but less than that seen with BL, while no pigment changes were noted with red light. A combination of red and blue light did not lead to synergistic effects on pigmentation. An increase in keratinocyte necrosis and p53 expression were noted in UVB-irradiated, but not BL-irradiated areas. No significant changes in melanin content or melanocyte number were noted among all groups, when compared to control at 24 hours and 7 days. Both UVB and red light produced oxidative stress, as measured by assessed by 8-oxoguanine labeling, in basal keratinocytes and perivascular fibroblasts.\textsuperscript{33}

Regazzetti et al determined that blue light-induced (415 nm, 5 to 90 J/cm\textsuperscript{2}) pigmentation in darker skin types results from activation of opsins 3, which activates pathways such as extracellular signal-regulated kinase and p38, leading to the phosphorylation of microphthalmia-associated transcription factor (MITF), tyrosinase activity, and subsequent melanogenesis in melanocytes.\textsuperscript{34}

\subsection*{1.3 Yellow Light (560-590 nm)}

\subsection*{1.3.1 In vitro study}

The effects of yellow light on markers of photoaging have been demonstrated to be photoprotective. Lan et al expanded on these findings by irradiating fibroblasts with yellow light (590 nm; 1 and 5 J/cm\textsuperscript{2}) alone, UVA alone (320-400 nm; peak wavelength 365 nm; 5 J/cm\textsuperscript{2}), or yellow light followed by UVA at the doses above. Yellow light increased cell viability and attenuated the expression of UVA-induced ROS and MMP-1. When compared to fibroblasts treated with the antioxidant N-acetylcysteine, similar effects were seen suggesting enhanced antioxidant effect of fibroblasts by yellow-light modulation.\textsuperscript{35}

\subsection*{1.3.2 Clinical study}

Weiss et al. treated 90 patients with photoaged skin using a full panel 590 nm non-thermal full face LED delivering 0.1 J/cm\textsuperscript{2} using the pulse sequence of 250 milliseconds “on” and 100 milliseconds “off” for each treatment for a total of eight treatments over four weeks.\textsuperscript{36} Digital imaging showed an improvement in signs of photoaging such as
periorbital rhytids, erythema, and pigmentation in 90% of patients. Of the 10 biopsy specimens obtained, an increase in collagen I deposition and reduced MMP-1 activity were noted in the papillary dermis.

1.4 | Red Light (620-750 nm)

The red light wavelength is the longest wavelength of the VL spectrum and has been reported to be restorative to the skin by stimulating cell growth, reducing inflammation, accelerating wound healing, and reducing skin fibrosis. Red light therapy (RLT) is typically employed through low level light therapy (LLLT, also known as photobiomodulation) in the form of LED or lasers, and generally contains the red or red to near infrared waveband (620-905 nm). As with yellow light, the evidence for the role of red light in photoaging is limited, but some studies have demonstrated photoprotective benefits and proposed mechanisms.

1.4.1 | In vitro studies

Human keratinocytes pretreated with phorbol-12-myristate-13-acetate (PMA) to induce inflammation and ROS, and subsequently irradiated with red light (625 nm), exhibited dose-dependent ROS-scaevenging and anti-inflammatory gene expression. The upregulation of Sphingosinekinase-1 (SPHK-1), a key molecule in sphingolipid metabolism that regulates the balance between cell proliferation and apoptosis, was also noted. In contrast, BL (425 nm) irradiation of PMA-treated keratinocytes did not demonstrate these beneficial effects. Moreover, pretreatment with red light may be photoprotective. Red light (620-690 nm; max 660 nm; 60 J/cm²) was found to upregulate genes involved in response to UVB (312 nm; 0.1 J/cm²)-induced oxidative stress, DNA damage, inflammation and wound healing in human dermal fibroblasts. While many studies demonstrate red light to be protective against photoaging, higher doses can potentially be toxic. For example, in a study by Hawkins et al, monolayers of fibroblasts, scratched with a sterile pipette to simulate a wound environment were irradiated with a helium neon laser (632.8 nm) at various doses (2.5-16 J/cm²) on two consecutive days demonstrated different dose-dependent outcomes. At a single dose of 5.0 J/cm² and two or three doses of 2.5 J/cm² increased cell migration and cell proliferation and maintenance of cell viability were observed, whereas exposures at 16 J/cm² produced the opposite effect. Red light (627 nm; 0.5-5 J/cm²) exposure can induce the anti-inflammatory cytokine, IL-4, in human keratinocytes and macrophage/dendritic cells through mechanisms not mediated by photo-oxidative mechanisms without the need for a photosensitizer, implicating its potential utility in phototherapy.

1.4.2 | Clinical study

Low level light therapy is also used for photorejuvenation. In a 10-patient cohort clinical study by Mezghani et al, LLLT (655 nm and 785 nm, average dose 27.77 J/cm² with the number of sessions dependent on the patient’s age) significantly reduced signs of facial skin aging, including wrinkles and the loss of firmness.

2 | DISCUSSION

Several effects of markers or clinical manifestations of photoaging have been identified in relation to VL exposure; however, the exact mechanism is still unknown. There are common themes among the studies reviewed. Shorter wavelengths of VL tend to have more deleterious effects on photoaging. Specifically, BL induces photoaging effects similar to ultraviolet radiation, such as erythema, inflammation, increase in ROS formation, and alterations of the ECM. It is also the shortest wavelength of VL that can induce pigmentation. The propensity of melanin and carotenoids to absorb BL over other VL wavelengths suggests BL absorption to be a consequence of evolutionary selection. Conversely, longer wavelengths of VL in the yellow and red spectrum, are often reported as protective against photoaging. Radiation dose also matters, regardless of wavelength, as high doses and cumulative exposure of red light can be deleterious, while low doses of BL or broad VL/VL+IR can be protective. See Table 1 for sunlight intensities of visible light wavelengths.

Each VL wavelength precipitates photoaging by a distinct mechanism. While high levels of ROS generated by photon absorption can be cytotoxic, low levels can function as signaling molecules, regulating cell growth. The latter effect serves as the premise for controlled redox balancing employed in laser therapy.

While many of VL-induced photoaging changes are similar to UVR clinically, the underlying pathophysiologic mechanisms may differ. Like UVR, VL can induce pigmentary changes, which can exacerbate pigmentary disorders, such as melasma. However, when compared to UVA1, VL has been found to induce a more prominent and long lasting pigmentation. These effects seem to be a synergy of UVA and VL as VL alone does not seem to have the same intensity and duration of pigmentation.

Although various complex mechanisms by which VL induces photoaging have been suggested, there are several limitations noted in the literature. One main issue is the inconsistency of wavelengths and irradiation protocols utilized among studies.
which precludes direct comparison of results from different studies. It is to be noted that irradiance (rate of radiation delivery) should be presented in any study on visible light. Additionally, studies often utilized irradiances that do not simulate natural sunlight exposure, or are orders of magnitude greater than the corresponding output from electronic devices.\textsuperscript{11,12} Generalizability of results from such studies to real life scenarios is thus limited. Lastly, given that most of the studies were conducted in vitro or in animals, extrapolating these results into the human population should be done with caution.

### 3 | CONCLUSION

Visible light wavelengths have been implicated in the process of photoaging. Different visible light wavelengths likely contribute to the beneficial and deleterious effects on photoaging by way of interaction with specific photoreceptors, ROS production, and other photon-mediated reactions. Further clinical studies are needed to determine the mechanism and action spectrum of VL-induced photoaging in humans, as well as optimal photoprotection with coverage against visible light wavelengths.

### ACKNOWLEDGEMENT

We would like to thank Steven J. Moore and Stephanie Stebens for their assistance on the literature review.

### CONFLICT OF INTEREST

Aaron Tisack and Angeli E. Torres have no relevant disclosures. Aunna Pourang is a subinvestigator for Biofrontera, L’Oreal, and Pfizer. Nneamaka Ezekwe is a subinvestigator for Biofrontera, L’Oreal, and Pfizer. Indermeet Kohli is an Investigator for Ferndale, Estee Lauder, L’Oreal, Unigen, Johnson and Johnson, Allergan and Bayer with grant received by the institution and is a Consultant for Pfizer, Johnson and Johnson, and Bayer with fee and equipment received by the institution. Iltefat Hamzavi has served as an advisory board member for AbbVie; a consultant for Incyte, Pfizer, and UCB; a principal investigator for AbbVie, Allergan, Bayer, Clinuvel Pharmaceuticals, Este Lauder, Ferndale Laboratories, Galderma Laboratories LP, GE Healthcare, Incyte, Janssen, Janssen Biotech, Johnson & Johnson, Lenicura, LEO Pharma, Pfizer, and Unigen; a subinvestigator for Amgen, Bristol-Myers Squibb, Foamix Pharmaceuticals, and Janssen; president of the HS Foundation; and co-chair of the Global Vitiligo Foundation. Henry W. Lim has served as investigator/co-investigator for research studies sponsored by Incyte, L’Oreal, Pfizer, and PCORI; he has served as a consultant for Pierre Fabre, ISDIN, Ferndale, Galderma, La Roche-Posay, and Beiersdorf; he has been a speaker on general education sessions for La Roche-Posay, and Cantabria Labs.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ORCID

Angeli E. Torres \textsuperscript{15} https://orcid.org/0000-0002-9551-2118

Indermeet Kohli \textsuperscript{15} https://orcid.org/0000-0002-2316-6375

### REFERENCES


