Direct and Indirect Effects of Blue Light Exposure on Skin: A Review of Published Literature

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Abstract

\textit{Background:} The growing use of electronic devices and other artificial light sources in recent decades has changed the pattern of exposure to blue light (400–500 nm). Although some progress has been made in the study of the biological effects of blue light on the skin, many questions in this field remain unexplored. The aim of this article was to review the currently available evidence on the deleterious effects of blue light on the skin as well as the methods and strategies designed to protect from the detrimental effects of blue light. The PubMed and ProQuest databases were searched in January 2022. Search results were supplemented by articles considered relevant by the authors. \textit{Summary:} The results of in vitro, in vivo, and clinical studies show that blue light produces direct and indirect effects on the skin. The most significant direct effects are the excessive generation of reactive oxygen and nitrogen species, and hyperpigmentation. Reactive oxygen and nitrogen species cause DNA damage and modulate the immune response. Indirect effects of blue light include disruption of the central circadian rhythm regulation via melatonin signaling and local circadian rhythm regulation via direct effects on skin cells. Antioxidants and sunscreens containing titanium dioxide, iron oxides, and zinc oxide can be used to protect against the detrimental effects of blue light as part of a strategy that combines daytime protection and night-time repair. \textit{Key Messages:} Blue light produces a wide variety of direct and indirect effects on the skin. As exposure to blue light from artificial sources is likely to continue to increase, this area warrants further investigation.

Introduction

Blue light is defined as light within the wavelength range of 400 nm (violet) to 500 nm (cyan) (Fig. 1) [1]. Blue light has lower energy than ultraviolet (UV) radiation (280–400 nm) and can reach further into the dermis, up to the depth of 1 mm [1, 2]. However, while the effects of UV radiation on skin have been widely studied, less is understood regarding the effects of blue light [3].

The sun is the main source of blue light, which is also emitted by electronic devices, such as computer moni-
tors, flat-screen televisions, smartphones, tablets, and fluorescent light bulbs (Table 1). Changing lifestyles, with less time spent outdoors and increased use of light-emitting diode (LED) and fluorescent lighting and electronic screens via smartphones, televisions, computer monitors, and laptops, have changed the pattern of blue light exposure in humans [3].

Although the full range and exact nature of the biological effects of blue light are unknown, both beneficial and detrimental effects have been described [5]. In controlled clinical settings, blue light can be used to treat conditions such as psoriasis, atopic dermatitis, and acne [5]. However, the field of blue light therapy is still developing, and its discussion is beyond the scope of this article. While most of the research to date has focused on the effects of blue light on the eyes, less is known about its impact on the skin, where similar photoreceptors are found. Finally, the consequences of increased blue light exposure during night-time hours and disruptions to circadian rhythms are not well understood.

Fig. 1. Solar radiation spectrum and depth of skin penetration. UV, ultraviolet.
The objectives of this review were to describe the evidence on the impact of blue light on the skin, understand the quality of evidence provided by existing medical research, and consider options for how the skin might be protected from the detrimental effects of blue light.

Search Methodology
The PubMed and ProQuest databases were searched in January 2022. Searches were restricted to clinical trials, systematic reviews, meta-analyses, and in vitro and in vivo studies reporting results in humans or non-clinical specimens. PubMed was searched using the term string ("blue light" OR "blue-light" OR "violet-blue light" OR "high-energy visible light") AND [skin OR

Table 1. Comparison of intensity of light emitted by devices and by the sun at wavelengths between 420 and 490 nm

| Source                          | Intensity, µW/cm² |
|---------------------------------|-------------------|
| Sun                             | 7,700             |
| TV LED (at 20 cm), Philips 55POS9002 | 78               |
| Laptop LED 1 (at 20 cm), Dell Inspiron 17 | 7.2         |
| Laptop LED 2 (at 20 cm), Dell Inspiron 24 | 15             |
| Computer screen (at 20 cm), Samsung P2270H | 22             |
| Cellular telephone (at 10 cm), Samsung 5G7 | 11             |

Adapted from Duteil et al. [4], with permission from Elsevier LED, light-emitting diode.
Table 2. Molecular and physiological mechanisms of direct blue light effects on the skin

| Cellular/molecular effects | Cell line/model organism/ participants | Wavelength, intensity | References |
|---------------------------|----------------------------------------|-----------------------|------------|
| ROS generation            | Medaka fish embryos                   | 445–465 nm at 50 J/cm² | Merino et al. 2020 [6] |
|                           | Human dermal fibroblasts               | 410 and 420 nm         | Opländer et al. 2011 [7] |
|                           |                                        | 420 nm at 1.0512 J/cm² (iPhone 6), 0.9684 J/cm² (iPhone 8+), or 0.7452 J/cm² (iPad, first generation) | Austin et al. 2018 [8] |
|                           |                                        | 450 nm at 30 mW/cm²     | Mignon et al. 2018 [9] |
|                           |                                        | 400–500 nm (peak at 450 nm) at 17.3 J/cm² for 6 h ≥400 nm and ≥450 nm at 120, 150, and 200 J/cm² | Morvan et al. 2019 [10] |
|                           | Reconstituted human epidermis          | 0.14% at 350–400 nm, 98.3% at 400–700 nm, 1.7% at 700–1,400 nm, and 0.3% at >1,400 nm at 65, 130, and 180 J/cm² | Mann et al. 2019 [11] |
|                           | Volunteers                             | 445–465 nm at 50 J/cm²  | Merino et al. 2020 [6] |
|                           |                                        | 400–480 nm at 45.6, 68.4, and 136.8 mJ/cm² | Liebel et al. 2012 [12] |
|                           | Artificially carbonylated porcine stratum corneum | 470 nm at 12 J/cm² | Mizutani et al. 2016 [13] |
|                           | Hairless mice                          | 460 nm (peak) at 44 mW/cm² | Nakashima et al. 2017 [14] |
|                           | HeLa cells                             | 462 nm (peak) at 520 µW/cm² + FMN/FAD | Yang et al. 2017 [15] |
|                           | NHEK                                   | 410 nm at 200 J/cm²     | Dong et al. 2019 [16] |
|                           |                                        | 445–465 nm at 50 J/cm²  | Merino et al. 2020 [6] |
|                           |                                        | 470–480 nm at 150 mW/cm² | Yoo et al. 2020 [17] |
| Carotenoid degradation    | Volunteers                             | 380–495 nm (peak at 440 nm) at 50 or 100 J/cm² | Vandervere et al. 2015 [18] |
|                           |                                        | 450±20 nm at 45 J/cm² for 5 consecutive days, 450±20 nm at 135 J/cm² single irradiation 440 nm (peak) at 100 J/cm² | Schütz et al. 2019 [19] |
|                           |                                        | 445–450 nm at 80 J/cm² | Mann et al. 2019 [11] |
| Flavin degradation        | Hairless mice                          | 460 nm (peak) at 44 mW/cm² | Nakashima et al. 2017 [14] |
|                           | Volunteers                             | 400–480 nm at 11 mW/cm² | Nakashima et al. 2017 [14] |
| DNA damage                | RPE                                    | 390–550 nm at 2.8 mW/cm² | Godley et al. 2005 [20] |
|                           | NHEK                                   | 410 nm at 300 or 600 J/cm² | Dong et al. 2019 [16] |
|                           |                                        | 415 nm at 4.8, 9.6, and 14.4 mW/cm² | Chamayou-Robert et al. 2022 [21] |
|                           | Reconstituted human epidermis          | 400–450 nm (peak at 427 nm) at 80 J/cm² | Bacheville et al. 2021 [22] |
|                           | Primary human keratinocytes and melanocytes, 2D culture | Blue light exposure for 60 or 120 min for 4 days (total intensity: 3.8 and 7.6 J/cm², respectively) | Kala et al. 2021 [23] |
| Whole-genome DNA          | Human keratinocytes, skin-derived endothelial cells | 450 nm at <100 J/cm² | Liebmann et al. 2008 [24] |
| methylation               |                                        | 410 nm at 20 or 30 J/cm², 420 nm at 20 and 30 J/cm², and 453 nm at 30 J/cm² | Opländer et al. 2011 [7] |
| Decreased proliferation   | Human dermal fibroblasts               | 450 nm at −5–60 J/cm² once per day for 3 days, and 500 nm at 20–60 J/cm² once per day for 3 days 445 nm at 50.5–91.8 J/cm² | Mignon et al. 2018 [9] |
|                           | Human keratinocytes                    | 470–480 nm at 68.4 and 136.8 mJ/cm² | Szymanski et al. 2021 [25] |
|                           |                                        | 470–480 nm at 68.4 and 136.8 mJ/cm² | Yoo et al. 2020 [17] |
### Table 2 (continued)

| Cellular/molecular effects | Cell line/model organism/participants | Wavelength, intensity | References |
|----------------------------|--------------------------------------|-----------------------|------------|
| Decreased expression of TP73 | Primary human keratinocytes and melanocytes, 2D culture | Blue light exposure for 60 or 120 min for 4 days (total intensity: 3.8 and 7.6 J/cm², respectively) | Kala et al. 2021 [23] |
| Decreased cell viability | RPE | 390–550 nm at 2.8 mW/cm² | Godley et al. 2005 [20] |
| | Human keratinocytes, skin-derived endothelial cells | 412–426 nm, 450 nm at <100 J/cm² | Liebmann et al. 2008 [24] |
| | Human dermal fibroblasts | 410 nm at 60 or 90 J/cm², and 420 nm at 60 or 90 J/cm² | Liebmann et al. 2010 [26] |
| | NHEK | 410 nm at 100 J/cm² | Opländer et al. 2011 [7] |
| | Primary human keratinocytes and melanocytes, 2D culture | Blue light exposure for 60 or 120 min for 4 days (total intensity: 3.8 and 7.6 J/cm², respectively) | Kala et al. 2021 [23] |
| Apoptosis | Jurkat cells | 453 nm at 60 or 100 J/cm² every 24 h for 3 consecutive days | Liebmann et al. 2010 [26] |
| | HeLa cells | 462 nm (peak) at 520 µW/cm² + FMN/FAD | Yang et al. 2017 [15] |
| | Human skin explants | 400–500 nm (peak at 450 nm) at 14.4 J/cm² for 5 h | Morvan et al. 2019 [10] |
| | Human dermal fibroblasts | 410 nm at 60 or 90 J/cm², and 420 nm at 60 or 90 J/cm² | Liebmann et al. 2010 [26] |
| | NHEK | 410 nm at 100 J/cm² | Opländer et al. 2011 [7] |
| | Primary human keratinocytes and melanocytes, 2D culture | Blue light exposure for 60 or 120 min for 4 days (total intensity: 3.8 and 7.6 J/cm², respectively) | Kala et al. 2021 [23] |
| Decreased ATP synthesis | Human dermal fibroblasts | 400–500 nm (peak at 450 nm) at 11.5 J/cm² for 4 h | Morvan et al. 2019 [10] |
| Decreased expression of genes regulating mitochondrial function (EGR1 and FOXO1) | Primary human keratinocytes and melanocytes, 2D culture | Blue light exposure for 60 or 120 min for 4 days (total intensity: 3.8 and 7.6 J/cm², respectively) | Kala et al. 2021 [23] |
| Increased EGFR phosphorylation | NHEK | 0.14% at 350–400 nm, 98.3% at 400–700 nm, 1.7% at 700–1,400 nm, and 0.3% at >1,400 nm at 65, 130, and 180 J/cm² | Liebel et al. 2012 [12] |
| Reduced EGFR levels | Human keratinocytes | 470–480 nm at 68.4 and 136.8 mJ/cm² | Yoo et al. 2020 [17] |
| Downregulation of TGF-β signaling | Human dermal fibroblasts | 450 nm at 2 and 30 J/cm² | Mignon et al. 2018 [9] |
| Increased proinflammatory cytokines | Reconstituted human epidermis | 0.14% at 350–400 nm, 98.3% at 400–700 nm, 1.7% at 700–1,400 nm, and 0.3% at >1,400 nm at 130 and 180 J/cm² | Liebel et al. 2012 [12] |
| | NHEK | 470–480 nm at 136.8 mJ/cm² | Yoo et al. 2020 [17] |
| | Human skin explants | 410 nm at 100–200 J/cm² | Dong et al. 2019 [16] |
| Increased COX-2 levels | Human skin explants | 400–500 nm (peak at 450 nm) at 17.3 J/cm² | Morvan et al. 2019 [10] |
| Delayed recovery of the epidermal permeability barrier | Hairless mice | 430–510 nm | Denda and Fuziwara 2008 [27] |
| MMP-1 release | Reconstituted human epidermis | 0.14% at 350–400 nm, 98.3% at 400–700 nm, 1.7% at 700–1,400 nm, and 0.3% at >1,400 nm at 65, 130, and 180 J/cm² | Liebel et al. 2012 [12] |
dermatology OR dermatologic OR cutis OR cutaneous OR epidermis OR dermis]), producing 1,106 results. ProQuest was searched using the term string ("blue light" OR "blue-light" OR "violet-blue light" OR "high-energy visible light") AND [skin or derma* OR cutis or cutaneous or epiderm* or dermis]) and (la. exact["English"]), producing 3,426 results. Titles and abstracts of identified articles were reviewed for inclusion. Search results were supplemented by articles considered relevant by the authors.

**Direct Effects of Blue Light**

Blue light exerts its direct effects on the skin by interacting with chromophores, in which it triggers a change from a ground state to an activated state [5]. Chromophores responsible for the direct effects of blue light include flavins, porphyrins, nitrosated proteins, and opsins (Fig. 2; Table 2) [5]. Activation of these molecules results in overproduction of reactive oxygen species (ROS) and release of reactive nitrogen species, i.e., nitrogen monoxide (NO), and hyperpigmentation [5].

**ROS Overproduction**

Multiple studies have shown that blue light exposure causes excessive ROS generation in cultured human keratinocytes and dermal fibroblasts, in medaka fish embryos, and in the skin of hairless mice and healthy human volunteers [6, 7, 9, 11–14, 16, 18–20]. The main chromophores responsible for blue light-induced ROS overproduction are believed to be flavins, such as flavin adenine

### Table 2 (continued)

| Cellular/molecular effects | Cell line/model organism/participants | Wavelength, intensity | References |
|---------------------------|--------------------------------------|-----------------------|------------|
| Decreased procollagen I content | Human dermal fibroblasts | 450 nm at 2 or 30 J/cm² | Mignon et al. 2018 [9] |
| Decreased collagen lattice contractility | Human dermal fibroblasts | 400–500 nm (peak at 450 nm) at 17.3 J/cm² for 6 h | Morvan et al. 2019 [10] |
| Increased protein carboxylation | Human skin explants | 460 nm peak at 14.4 J/cm² | Morvan et al. 2019 [10] |
| Hyperpigmentation | Normal human melanocytes | 415 nm | Regazzetti et al. 2018 [28] |
| | Abdominoplasty skin (phototype IV) Volunteers | 415 nm at 5–90 J/cm² | Regazzetti et al. 2018 [28] |
| | Female volunteers (phototypes III and IV) | 450±20 nm at 45 J/cm² for 5 consecutive days, 450±20 nm at 135 J/cm² single irradiation, 420–500 nm (peak at ∼450 nm) at 60 J/cm² for 4 consecutive days | Schütz et al. 2019 [19] |
| Photolytic release of NO from nitrosated proteins | Human keratinocytes, skin-derived endothelial cells BSA 2% in PBS | 450 nm at <100 J/cm² | Liebmann et al. 2008 [24] |
| | NHEK | 410 nm at 30 J/cm² | Kim et al. 2016 [30] |
| Decreased expression of antimicrobial peptides | Human keratinocytes, skin-derived endothelial cells | 412–426 nm, 450 nm at <100 J/cm² | Liebmann et al. 2008 [24] |
| Stimulation of proliferation and differentiation | Human keratinocytes, skin-derived endothelial cells Human keratinocytes | 453 nm at 66 or 100 J/cm² every 24 h for 3 consecutive days | Liebmann et al. 2010 [26] |

2D, two-dimensional; ATP, adenosine triphosphate; BSA, bovine serum albumin; COX-2, cyclo-oxygenase-2; EGFR, epidermal growth factor receptor; EGR1, early growth response protein 1; FAD, flavin adenine dinucleotide; FMN, flavin mononucleotide; FOXO1, forkhead box protein O1; MMP-1, matrix metalloproteinase-1; NHEK, normal human epidermal keratinocytes; NO, nitric oxide; PBS, phosphate-buffered solution; ROS, reactive oxygen species; RPE, retinal pigmented epithelium; TGF-β, transforming growth factor-β.
Blue Light Effects on Skin

Blue light effects on skin are significant and can lead to cellular damage, hyperpigmentation, altered gene expression, and mitochondrial dysfunction. Several studies have found that blue light-induced ROS generation was mostly restricted to the mitochondria, damaging mitochondrial DNA and disrupting respiration [9, 14, 20]. Furthermore, blue light has been shown to decrease the expression of genes regulating mitochondrial function, such as early growth response protein 1 (EGR1) and forkhead box protein O1 (FOXO1), in primary human keratinocytes and melanocytes [23]. However, other studies have shown that ROS produced as a result of blue light exposure can also damage nuclear DNA [16, 20]. Importantly, Chamayou-Robert et al. [21] have shown that blue light has clastogenic and aneugenic effects in human keratinocytes, resulting in stable and heritable aberrations. Blue light exposure has been shown to reduce flavin autofluorescence in the skin of human volunteers [14].

In addition to flavins and porphyrins, Mizutani et al. [13] have shown that both UV and blue light induce ROS generation from carbonylated proteins located in the stratum corneum. They found that ROS generation was induced by radiation in the range between 360 and 470 nm, suggesting that blue light has a greater contribution to ROS generation from carbonylated proteins located in the stratum corneum than UV [13]. Furthermore, Morvan et al. [10] have shown that blue light induces protein carbonylation in human skin explants. In experiments on hairless mice, blue light delayed permeability barrier recovery and reduced the thickness of the lipid layer located between the stratum corneum and stratum granulosum [27].

Blue light-induced ROS overproduction is associated with decreased cell viability and/or cell proliferation, increased proinflammatory signaling, and disrupted cell metabolism [7, 10, 12, 16, 17, 20]. Dermal fibroblasts exposed to blue light exhibited general metabolic inhibition, reduced adenosine triphosphate (ATP) synthesis, impaired transforming growth factor-β (TGF-β) signaling, reduced procollagen I synthesis, and reduced collagen lattice contractility [9, 10]. Yoo et al. [17] showed that blue light suppressed proliferation in human keratinocytes by increasing the expression of the transient receptor potential vanilloid 1 (TRPV1) and downregulating the epidermal growth factor receptor (EGFR)/phosphoinositide 3-kinase (PI3K)/AKT/forkhead box O3a (FOXO3a) pathway. They have also shown that blue light causes an increase in ROS and tumor necrosis factor-α (TNF-α). Blue light also suppressed the expression of TP73, a gene involved in proliferation, in primary human keratinocytes and melanocytes [23]. Dong et al. [16] reported that, in addition to ROS overproduction, blue light irradiation increased the levels of proinflammatory cytokines interleukin (IL)-1α, IL-6, IL-8, and TNF-α in cultured human keratinocytes. The study by Liebel et al. [12] demonstrated that visible light irradiation of reconstituted human epidermis resulted in increased IL-1α and matrix metalloproteinase-1 (MMP-1) release. Morvan et al. [10] reported that blue light exposure increased cyclooxygenase-2 (COX-2) expression in human explants.

Reactive Nitrogen Species Overproduction

Blue light can cause photolysis of nitrosated proteins, but only in the presence of cupric ions (Cu²⁺), as blue light alone does not have the energy needed to break the covalent bond in N–O [31]. As a result of this reaction, NO is released, which induces differentiation in skin cells [24, 26, 30]. Liebmann et al. [24] have demonstrated that at wavelengths of 412–426 nm and high fluences, blue light is cytotoxic to human keratinocytes and skin-derived endothelial cells [26]. However, at 453 nm and at fluences of up to 500 J/cm², blue light inhibits proliferation by inducing differentiation, as shown by increased levels of involucrin and keratin-1 messenger RNA (mRNA) [26]. In a study conducted by Kim et al., blue light inhibited innate immune responses in human keratinocytes by inducing the S-nitrosylation of various proteins, including TIR-domain-containing adapter-inducing interferon-β (TRIF), Myd88, and nuclear factor-κ light chain enhancer of activated B cells (NF-κB) [30]. Blue light irradiation also blocked Toll-like receptor (TLR) 3- and TLR5-induced NF-κB phosphorylation, resulting in reduced levels of TLR-induced proinflammatory cytokines [30]. In humans, photolytic release of NO from nitrosated proteins is believed to be sufficient to cause significant local vasodilation and possibly even to reduce systemic blood flow [31].

Hyperpigmentation

Blue light is capable of causing pigmentation and hyperpigmentation of the skin, the latter of which can lead to mottled hyperpigmentation or age spots [19, 29]. A study conducted on 20 volunteers with skin types IV–VI found that, compared with UV, blue light produced darker hyperpigmentation that lasted longer [32]. While both UV and blue light cause hyperpigmentation via ROS generation, only blue light causes hyperpigmentation via opsin stimulation [10]. In skin biopsies from healthy volunteers, blue light irradiation over 5 consecutive days re-
sulted in increased perinuclear vacuolization in keratinocytes and an increased number of melan-A-positive cells [10, 33]. Blue light irradiation increased melanin production, oxygen saturation, and hemoglobin content in female volunteers [29]. Skin darkening and erythema have also been observed after exposure to blue light [29, 34].

Opsins are a class of photosensitive G protein-coupled receptors, which regulate various signaling cascades [5]. In addition to the retina, opsins are expressed in the skin (Table 3) [5].

For example, Kim et al. [39] reported that rhodopsin is found in the plasma membrane of cultured human keratinocytes. The authors also showed that blue light irradiation increases rhodopsin expression, which, in turn, decreases the expression of keratinocyte differentiation markers keratin-1 and keratin-10 via the Gαi pathway [39]. On the other hand, Gondran et al. [40] reported that blue light exposure reduced the levels of opsin (OPN) 1 short wave (OPN1 SW), OPN2, and OPN3 in cultured human keratinocytes.

Regazzetti et al. [28] identified OPN3 as the only opsin that was expressed at a significant level in human melanocytes. When exposed to blue light, OPN3 initiated a signaling cascade that included calcium-dependent activation of calcium/calmodulin-dependent protein kinase II (CAMKII), followed by activation of cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), extracellular signal-regulated kinase (ERK) and p38, leading to phosphorylation of microphthalmia-associated transcription factor (MITF) and, finally, increases in the enzymes tyrosinase and dopachrome tautomerase (DCT) that are responsible for melanogenesis [28]. Blue light-induced hyperpigmentation is more pronounced and persistent in people with darker skin (Fitzpatrick types III–VI), likely because they have higher levels of tyrosinase–DCT complexes than people with lighter skin (Fitzpatrick types I and II) [1].

**Indirect Effects of Blue Light**

In addition to directly affecting the skin, blue light can exert indirect effects on the body by disrupting the nor-

| Cellular/molecular effects | Cell line/participants | Wavelength, intensity | References |
|----------------------------|------------------------|-----------------------|------------|
| Decreased plasma melatonin | Volunteers             | 420 nm at ≥11 µW/cm², 460 nm for 90 min Room light (≤200 lux, 4100 K) during sleep hours | Brainard et al. 2008 [35], Gooley et al. 2011 [36] |
| Delayed melatonin onset    | Volunteers             | Room light (<200 lux, 4100 K) for 16 h per day Blue-enriched white light (250 lux, 9000 K, 0.087 mW/cm²) | Gooley et al. 2011 [36], Gabel et al. 2017 [37] |
| Decreased melatonin duration | Volunteers           | Room light (<200 lux, 4100 K) for 16 h per day | Gooley et al. 2011 [36] |
| Decreased melatonin exposure | Younger volunteers (mean age 25.0 years) | Blue-enriched white light (250 lux, 9000 K, 0.087 mW/cm²) | Gabel et al. 2017 [37] |
| Decreased subjective sleepiness | Volunteers         | Blue-enriched white light (250 lux, 9000 K, 0.087 mW/cm²) | Gabel et al. 2017 [37] |
| Decreased proximal skin temperature | Volunteers | Blue-enriched white light (250 lux, 9000 K, 0.087 mW/cm²) | Gabel et al. 2017 [37] |
| Increased cortisol level   | Older volunteers (mean age 63.6 years) | Blue-enriched white light (250 lux, 9000 K, 0.087 mW/cm²) | Gabel et al. 2017 [37] |
| Decreased per1 transcription | NHEK                 | 410 nm at 100 J/cm² | Dong et al. 2019 [16] |
| Alteration of the ECTO-NOX oscillatory pattern | Murine skin explants | 495 nm for 2 min | Morré and Morré 2003 [38] |
| Decreased keratin-1 and keratin-10 | NHEK                 | 410 nm (peak) at 10 or 50 J/cm² | Kim et al. 2013 [39] |
| Elastic fiber network disruption | Skin biopsies      | Not specified | Gondran et al. 2016 [40] |

ECTO-NOX, external nicotinamide adenine dinucleotide phosphate oxidase; NHEK, normal human epidermal keratinocytes.
Blue Light Effects on Skin

The circadian rhythm has been shown to affect multiple cellular and physiological processes occurring in the skin [41]. For example, the rate of blood flow, permeability to both hydrophilic and lipophilic compounds, and transepidermal water loss are all higher in the evening and at night than during the day [41]. On the other hand, sebaceous gland activity is highest during the day and decreases in the evening and at night [41]. Therefore, moisturizers and topical medications, such as corticosteroids, are more effective when used later in the day. Normal keratinocyte proliferation peaks at night, and this periodicity is lost in cancerous skin cells [41]. Interfollicular epidermal keratinocytes and hair follicle keratinocytes obtained from women with circadian rhythm dysregulation due to shift work have been shown to have reduced clonogenic potential [43]. Repair of sunlight-induced DNA damage also mostly occurs at night. One exception is the enzyme 8-oxoguanine DNA glycosylase (OGG1), which is involved in the base excision repair pathway and is most active in the morning. OGG1 levels are decreased in shift workers, suggesting that healthy sleep is required for its optimal functioning [41]. Therefore, the circadian rhythm influences multiple processes occurring in the skin, with most of the repair and regeneration taking place at night [41, 42].

Protecting Skin from Blue Light Exposure

Carotenoids are one of the main classes of antioxidants that protect the skin from ROS damage. Most of the carotenoids found in the skin absorb radiation in the blue section of the spectrum. The highest concentration of carotenoids in the skin is found in the lipid lamellae located in the stratum corneum, the outermost skin layer that serves as a permeability barrier, preventing transepidermal water loss [13, 44]. Several studies have shown that blue light irradiation causes degradation of carotenoids [11, 18, 19].

Most currently available sunscreens are designed to protect against UV radiation, and organic sunscreen agents predominantly absorb UVB radiation [34]. Tinted sunscreens that contain inorganic compounds such as iron oxides, titanium dioxide, and zinc oxide are able to provide protection against blue light radiation [34, 45]. When considering cosmetic interventions for protecting against blue light, a strategy of daytime protection and night-time repair may be optimal. An ideal regimen of daytime protection would include reduced exposure to...
Table 4. Defense pathways and methods that could be targeted to offer protection from blue light to skin

| Pathway                              | Method of protection                          | Available or investigational agents                                                                 |
|--------------------------------------|-----------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Prevention/reduction of blue light exposure | Sunscreen                                    | Iron oxide 3.2% [34]                                                                                |
|                                      |                                               | Microfine titanium dioxide 13.4% or 18% [48]                                                        |
|                                      |                                               | Zinc oxide 5%, pigmented grade titanium dioxide 4% [47]                                             |
|                                      |                                               | Total Eye® 3-in-1 Renewal Therapy, SPF 35 (titanium dioxide 7.9%, zinc oxide 6.7%, and black [CI: 77499], yellow [CI: 77492], and red [CI: 77491] iron oxides), All Calm® Clinical Redness Corrector, SPF 50 (titanium dioxide 11.6%, zinc oxide 8.6%, and black [CI: 77499], yellow [CI: 77492], and red [CI: 77491] iron oxides), Even Up® Clinical Pigment Perfector®, SPF 50 (titanium dioxide 11.6%, zinc oxide 8.6%, and black [CI: 77499], yellow [CI: 77492], and red [CI: 77491] iron oxides) [46] TriAsorB [22] Topical cream (active carotenoids, capsanthin, and capsanthin esters) [49] Ethyl ascorbyl ether-containing cream [50] PEPHA®-AGE (Scenedesmus rubescens extract), Seactive-ZT (Zonaria tournefortii extract) [51] Parsol® Max (methylene bis-benzotriazolyl tetramethylbutylphenol, aqua, decyl glucoside, propylene glycol, xanthan gum), Parsol® TX (titanium dioxide, silica, dimethicone), Parsol® ZX (zinc oxide, triethoxycaprilylsilane), TNP45TELR (titanium dioxide, C12–15 alkyl benzoate, stearic acid, silica, alumina, polyhydroxystearic acid) [51] Aqua Ceria (cerium oxide, platinum powder, water), Covabead® Crystal (calcium sodium borosilicate) [51] |
| Hyperpigmentation                     | Blue light filter                              | Oral lutein/zeaxanthin, antioxidant complex containing lycopene, beta-carotene, alphatocopherol, and selenium [55] |
|                                      | Tyrosinase inhibition                          | Ellagic acid-rich pomegranate extract [55]                                                          |
|                                      | Antioxidant                                    | Polypodium leucotomos extract [55]                                                                 |
| Stratum corneum barrier integrity    | Inhibition of plasmin and urokinase            | BSFAB [54]                                                                                          |
|                                      | Improved transglutaminase 1 expressions         |                                                                                                     |
| ROS generation, hyperpigmentation    | Antioxidant                                    | Deschampsia antarctica aqueous extract [56]                                                         |
|                                      |                                               | Vitamin B3 [57]                                                                                     |
|                                      |                                               | Lutein [57]                                                                                         |
|                                      |                                               | Coenzyme Q10 [57]                                                                                   |
|                                      |                                               | Scenedesmus rubescens extract [57]                                                                 |
|                                      |                                               | Alto Defense Serum™ [58]                                                                             |
|                                      |                                               | Niacinamide                                                                                         |
|                                      |                                               | ET-VC™ (3-O-ethyl ascorbic acid)                                                                    |
|                                      | Antioxidant Nrf2 inducer                       | Licochalcone A 1 μmol/L [11]                                                                        |
blue light and prevention or minimization of free radical formation (Table 4) [22, 34, 46–51]. An ideal regimen of night-time repair would include greater protection of the opsin photoreceptors against activation, collagen against degradation, mitochondria against damage, and DNA against oxidation, as well as other methods (Table 4) [11, 29, 51–61].

Limitations
The scientific understanding of the effects of blue light on the skin has improved in recent decades. However, several factors continue to limit the progress in this field, including variations in the definition of blue light itself. Methodological constraints include the use of different light sources, which often produce radiation outside blue light wavelengths, precluding the establishment of firm cause–effect connections and complicating comparisons between studies. Another limitation is the lack of understanding of the biological significance of the differences in the intensity of blue light radiation between natural and artificial sources. Furthermore, some authors contend that the magnitude and duration of exposure to blue light produced by the sun, indoor lighting sources, and various electronic devices in the course of normal day-to-day activities are insufficient to produce meaningful biological effects or to worsen lesions in melasma patients [4, 62]. While the intensity of blue light exposure from the sun is significantly higher than that generated by the screens of electronic devices, some chromophores, such as melanopsin, are particularly sensitive to blue light, and even low levels of irradiation may be able to induce significant effects [5]. Lastly, there is a lack of a widely adopted indicator of the ability of sunscreens to protect against blue light radiation. The sun protection factor (SPF), a common marker of sunscreen effectiveness, primarily reflects the UVB protection level [34]. The SPF shows how much energy is required to produce sunburn on sunscreen-protected skin compared with unprotected skin. Moseley et al. [47] developed a modified SPF, which they termed photosensitivity protection factor (PPF), which reflects the effects of visible-spectrum radiation on the skin of patients with photosensitivity to such radiation. However, a blue light-specific metric is still lacking.

Conclusions
Blue light is capable of producing various effects on the skin, including deleterious direct effects, such as hyperpigmentation and photoaging, and complex indirect effects, such as circadian rhythm modulation. The precise nature of how blue light affects the circadian rhythm is not fully understood. However, increased exposure to blue light due to the widespread use of electronic devices warrants further research attention, particularly because long-term exposure to artificial sources of blue light has the potential to produce clinical effects by altering mela-

### Table 4 (continued)

| Pathway               | Method of protection                        | Available or investigational agents                                                                 |
|-----------------------|---------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Antioxidant MMP-1 suppressor | Indian sandalwood (*Santalum album*) oil [59] |                                                                                                    |
| MMP-1 suppressor       | Arctalis™ (*Pseudoalteromonas* ferment extract) [51] |                                                                                                    |
| Antioxidant OPN3 inhibitor | Fernblock® (*Polypodium leucotomos* aqueous extract) [60, 61] |                                                                                                    |
| Antioxidant OPN3 inhibitor MMP-1 suppressor | Active complex (*Lespedeza capitata* flower/leaf/stem extract, *Polypodium leucotomos* aqueous extract and acrylic acid/acylamidomethyl propane sulfonic acid copolymer) [52] |                                                                                                    |
| Photoaging            | Increased collagen content                   | 11β-HSD1 inhibitors [53]                                                                            |

11β-HSD1, bi-aryl amide 11β-hydroxysteroid dehydrogenase 1; BSFAB, benzyisulfonyl-D-Ser-homoPhe-(4-amidinobenzylamide); MMP-1, matrix metalloproteinase-1; Nrf2, nuclear factor erythroid 2-related factor 2; OPN3, opsin 3; ROS, reactive oxygen species; SPF, sun protection factor.
tonin signaling. Progress in this field is hampered by a lack of standardized methods, including the use of different sources of blue light and measures of its biological effects. Several strategies designed to protect against the negative effects of blue light are being explored, of which the most promising include daytime protection and night-time repair components.

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Orawan Suitthimeathegorn performed the literature review, constructed the outline, and wrote the manuscript. Cheng Yang, Yanyun Ma, and Wei Liu shaped the outline and reviewed the manuscript. All the authors edited and approved the final revision of this paper for submission.

**Data Availability Statement**

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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