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Review Article

Illuminating Healing: A Comprehensive Review of Blue and Red Light Therapy Applications and Efficacy

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A B S T R A C T

In this study we have assessed the use of blue light (peaking at 415 nm), blue light (approximately 700 nm), and a blue and red light mixture (peaking at 415 and 660 nm) in the treatment of psoriasis, acne vulgaris, diabetes, cancer, actinic keratosis, seasonal affective disorder, and Candida albicans infections. The use of light with wavelengths between 400 and 1100 nm to encourage tissue repair, lower inflammation, and enhance analgesia is known as photobiomodulation (PBM). Red and near-infrared (NIR) light have long been used therapeutically, but new research suggests that blue and green light, among other visible spectrum wavelengths, may also be helpful. The purpose of this review is to assess the research on the possible therapeutic benefits of PBM, with a focus on the effects of red and blue light. This review emphasizes how, depending on the light's wavelength, PBM can have a wide range of effects on the body's various chromophores. The necessity of disclosing exposure and treatment data is still emphasized because doing so will allow for direct comparisons between trials and, ultimately, the identification of PBM's full potential.

Keywords: Red light, Blue light, PBM, Acne.

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INTRODUCTION:

With the goal of producing a positive outcome, light treatments employ light with various characteristics (wavelength, intensity, coherent or incoherent light) [1]. Blue light, red light, and a mix of blue and red light are among the light-based acne therapies [2]. Light is vital to human health and initiates a variety of physiological processes [3]. The proportions of the sun's electromagnetic energy that reach the earth are separated into three primary zones [4]. These areas include visible light (400–760 nm), infrared light (760–1000 nm), and ultraviolet (UV) light (280–400 nm). Because of the variety of biological photoacceptors [5], UV radiation's photoreactivity, and the cell-specific reactions [6] it triggers, its effects on mammalian cells have been thoroughly studied [7]. It has been demonstrated that red and near-infrared (NIR) wavelengths are advantageous, and new research suggests that other visible spectrum wavelengths, such as blue light (400–500 nm), may also be advantageous. Numerous bacteria are less likely to become resistant to blue light treatment, making it a good substitute for antibiotic therapy, according to reports of the antibacterial activity and susceptibility of blue light on multiple strains of the same bacterium [8]. The sun is the primary source of blue light, which is present throughout our surroundings [9]. Daytime exposure to blue light is essential for maintaining the balance of our biological needs and has both visual and nonvisual effects on our bodies and minds, primarily regulating human behavior and circadian rhythm [10,11]. Between 400 and 700 nm, visible light makes up about half of the sunshine that reaches the earth's surface. Flash lamps, light-emitting diodes, and lasers are additional sources of visible light. Photoreceptive chromophores (such as melanin, heme, and opsins) absorb photons from visible light, which activates and supplies energy to chromophores, changing skin function [12]. A certain wavelength of light combined with a photosensitizer is used in photodynamic therapy (PDT), a therapeutic

approach. To verify the effectiveness of PDT and its potential as an alternative treatment, this study used blue light in addition to red light, which is frequently employed in human medicine, to the microorganisms that cause skin infections using photosensitizers [13]. PDT works by activating a photosensitizing agent with visible light, which then combines with oxygen to produce a cytotoxic product [14].

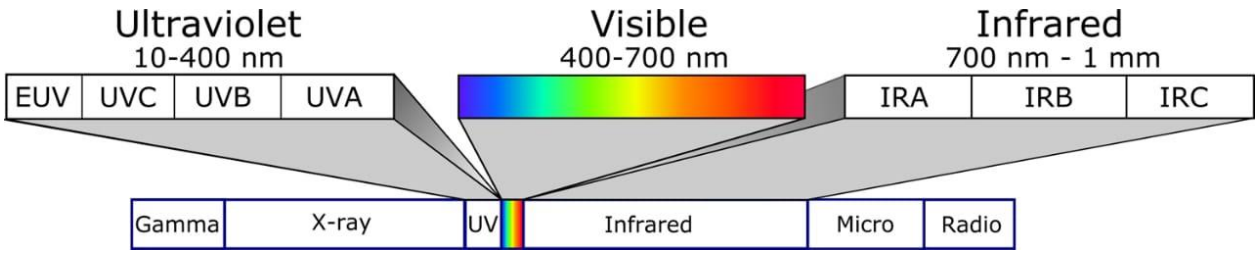

Figure 1: Electromagnetic radiation spectrum. UVR, VL, and IR are optical radiation. VL can be divided by color: blue/violet (400-500 nm), green (500-565 nm), yellow (565-590 nm), orange (590-625 nm), or red (625-700 nm). Similarly, UVR is separated into separate spectra: UVA (320-400 nm), UVB (290-320 nm), Ultraviolet-C (200-290 nm), and extreme (EUV; 10-120 nm). IR can be subdivided into infrared-A (near-IR; 700-1440 nm), IRB (mid-IR; 1440-3000 nm), and IRC (far-IR; 3000 nm-1 mm) wavelengths. Spectral boundaries are not discrete, and there is an overlap in the biologic effects between adjacent forms of EMR [12].

Sources of Red and Blue light:

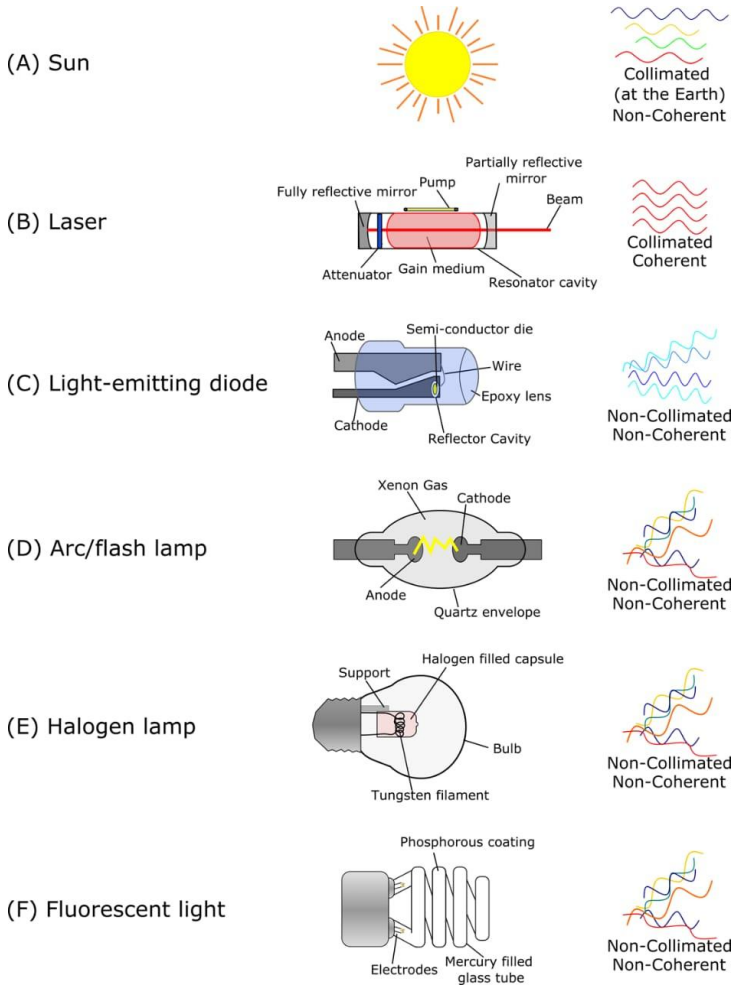

Figure 2: Diagram of natural and artificial visible light sources [12].

Potential mechanisms of blue-light treatment:

It has been shown that by momentarily binding the light-sensitive ligand optovin, short-wavelength BL selectively activates zebrafish TRPA1 cation channels [15]. The same wavelength of low-intensity light causes pain on the skin of healthy volunteers [16]. Furthermore, BL up to 460 nm in wavelength may activate human TRPA1 and pre-sensitized TRPV1 channels in transfected HEK 293 T cells [16,17]. The activation of TRPA1 and TRPV1 channels, located at unmyelinated C and small myelinated Ad fibers, results in the production of proinflammatory cytokines [18,19]. Vasodilatation and protein extravasation, which are crucial events in nociceptor sensitization and neurogenic inflammation, are brought on by the neuropeptide's substance P and calcitonin gene-related peptide [16,20]. Consequently, TRPA1 and TRPV1 have been suggested to be important in neurogenic inflammation and chronic pain [16,21-23]. It is interesting to note that reactive oxygen species, which also

activate TRPA1 (16), cause photosensitization and an increased pain response to BL treatment. In a human surrogate model of chronic pain, we have discovered that extended illumination has an antinociceptive effect, despite the fact that short-term BL stimulation has been demonstrated to be nociceptive. On the one hand, this discovery might be explained by the excitation state of the nociceptive fibers. Similar to chronic pain disorders, electrical stimulation causes nociceptive fibers to constantly depolarize. If BL light further activates previously sensitive TRPA1 and TRPV1 cation channels, it may cause hyperpolarization of activated nociceptive fibers, which could result in cation outflow instead of influx. Long-term BL illumination may alternatively desensitize nociceptive fibers, as has been shown for a number of TRP agonists [24-27]. Lastly, it has been shown that BL increases the antioxidative capacity of human skin fibroblasts, which may facilitate further antinociceptive effects [28,29]. The optimal level and duration of BL's nociception-affecting effects, especially in people with chronic pain, require more investigation [30].

Potential mechanisms of red-light treatment

Primary mechanisms of PBM: According to the Grotthuss–Draper law, often known as "The First Law of Photochemistry," a system's capacity to absorb light is a necessary condition for photochemical reactions. This section then reviews the literature on the most often proposed cellular photoacceptors (chromophores) that are thought to mediate the biological effects in PBM. We address the possible photoacceptors responsible for green and blue light wavelength transduction [31].

Secondary mechanisms of PBM: Examining the possible explanations for the primary PBM processes reveals that several routes converge on the production of the same signaling molecules, including ROS. Thus, this review portion evaluates the possible influence of PBM on ROS-related pathways. Note that this assessment evaluates the impact of PBM on multiple downstream targets. PBM may control a varying number of these targets, depending on the light's wavelength, the amount to be taken and in vitro/in vivo structure. This is also true for the primary mechanisms of PBM [31].

Therapeutic Applications:

Acne: Clinical investigations showed that BL and RL from devices at 400–445 nm and 625-700 nm, respectively, improved mild to moderate acne by decreasing Cutibacterium acnes colonization, pore size, and inflammation [32-34,12].

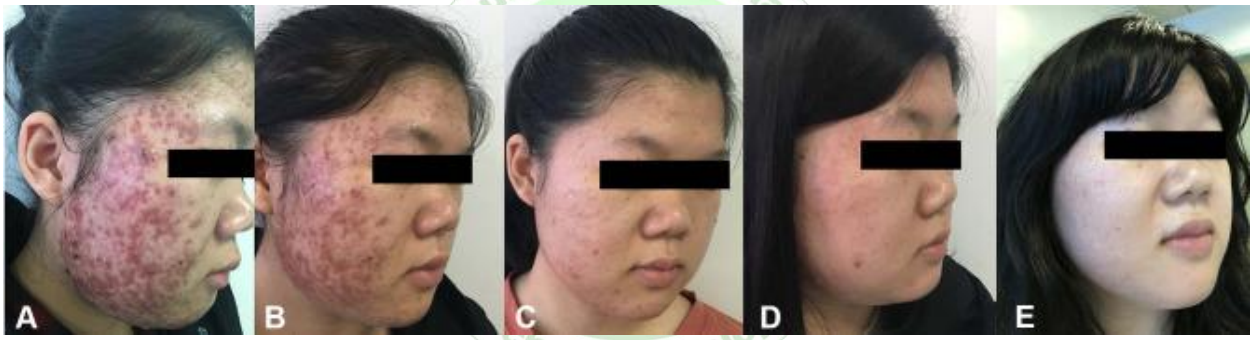

Figure 3: (A) Before treatment. (B) After the end of red and blue light treatment (at second week). (C) After RF treatment (at tenth week). (D) after 2 times of IPL treatments (the 18th week). (E) After 4 times of IPL treatments (the 26th week) [35].

Blue light can rapidly destroy C. acnes through a chemical mechanism that produces singlet oxygen, which has anti-inflammatory qualities and reduces acne inflammation damage [36]. Red light can reduce or even eliminate erythema, which helps to restore skin smoothness and avoid postacne scarring, while also reducing inflammation and promoting collagen synthesis and tissue regeneration [37, 35]. Phototherapy of acne vulgaris employing a blue light-emitting source more suitable to the absorption spectrum of porphyrins might provide a therapeutic response with a lower irradiation dose and avoid the potential risks of UV radiation [38]. Visible light therapy is a noninvasive, safe, and effective treatment for acne vulgaris [39].

Cancer: Protoporphyrins preferential uptake and accumulation in malignant tissue is exploited by blue light cystoscopy (BLC), a photodynamic diagnostic technique. BLC, sometimes referred to as the fluorescence-based photodynamic diagnostic method, takes use of the preferential uptake and accumulation of protoporphyrins in neoplastic tissue [40,41,42]. BLC significantly increases the detection rate of CIS and small Ta lesions that WLC missed, according to a number of studies and subsequent meta-analyses [40-44]. Furthermore, residual tumor rates are nearly tripled when BLC is utilized in place of WLC alone [42-46].Photodynamic therapy (PDT) has proven to be an effective treatment for dermatological malignancy [47, 48].

Actinic keratosis (AK): The clinical hallmark of actinic keratosis (AK), a kind of in situ squamous cell carcinoma (SCC) that arises in areas of the skin that are frequently exposed to the sun, is erythematous, scaly, or crusty patches of skin [49]. Actinic keratosis (AK), which develops on skin exposed to the sun for a long time, is one of the most common disorders doctors treat [50]. Topical photodynamic treatments (PDT) are strongly recommended for patients with confluent AK lesions or field cancerization because untreated lesions can progress to invasive SCC [49,51]. Recent recommendations state that PDT is a preferred treatment option because of its exceptional efficacy and remarkable cosmetic outcomes [52-54]. Photodynamic therapy (PDT) has been approved by the Food and Drug Administration (FDA) for the spot treatment of actinic keratoses (AKs) using either aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), which is converted to ALA in the skin [55]. Blue light (417 +- 5 nm) and red light (630 +-2 nm) are approved

for use with ALA and MAL, respectively, despite the fact that protoporphyrin IX (PpIX), the photosensitizing metabolite of ALA produced in the epidermis after topical application of the prodrug, is activated by both wavelengths as well as broadband visible light and sunlight [55,56].

Psoriasis: Innovative medications are still needed to treat psoriasis. The ineffectiveness and cumulative toxicity of topical treatments, as well as those of phototherapy and systemic treatments, significantly restrict the available therapeutic options. As a safe alternative to ultraviolet (UV) phototherapy for the treatment of inflammatory skin conditions, visible light phototherapy has drawn increased attention from dermatologists in recent years. The absorption of visible light or UV radiation by skin chromophores is the primary vehicle via which light'sbiological effects on the skin start [57].

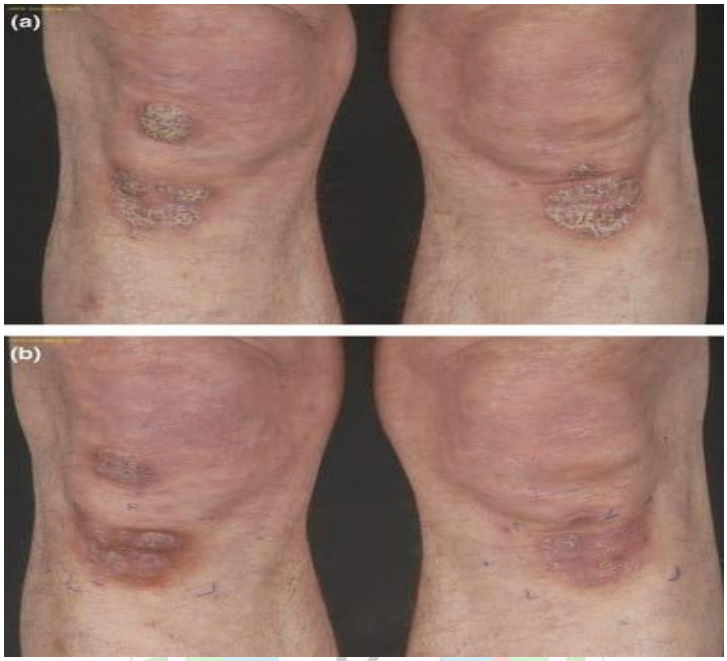

Figure 4: Before (a) and after (b) treatment photos of psoriasis plaques treated with blue (right leg) and red light (left leg) [57].

Candida albicans Infections: The most prevalent fungus is Candida albicans [58-60]. Even while fungal infections have become more common over the past few decades, there are currently not many effective antifungal drugs on the market [61]. Topical antifungal drugs like clotrimazole are the best option for treating cutaneous C. albicans infections. However, there is evidence of clotrimazole resistance in Candida albicans [62,63], and antifungal drug resistance may be increasing [64,65]. Therefore, there is an urgent need to discover new antifungal therapy techniques. A harmless dye known as a photosensitizer (PS) can be preferentially localized in specific tissues or cells, according to the theory underlying photodynamic treatment (PDT). The cells that have bound the PS may be killed by reactive oxygen species (ROS), which are produced when harmless visible light activates the PS. Numerous published studies have demonstrated that PDT is highly effective at inactivating fungi in vitro [66-68]. Additionally, it is believed that bacteria becoming resistant to PDT is an uncommon occurrence because PDT is typically a multitarget process, which distinguishes it from the bulk of other antifungal drugs [69,70].

Seasonal affective disorder (SAD): A decrease in mood in the fall and/or winter, followed by a spontaneous remission in the spring or summer, is the hallmark of the illness known as seasonal affective disorder (SAD). The DSM-IV classifies seasonal major depression with recurrent episodes (DSM-IVR) as a subtype of SAD. However, compared to the usual symptoms of decreased appetite and insomnia that are normally observed in significant depression, SAD patients tend to display more atypical symptoms, such as hyperphagia and hypersomnia. While the exact origin of SAD is yet unknown, seasonal variations in the photoperiod seem to be linked to mood and symptom fluctuations. Indeed, it has been proposed that remission is brought on by an increase in light exposure in the spring and summer, whereas SAD is brought on by a decrease in light exposure in the fall and winter. Bright light (BL) administration was consequently recommended and approved as the recommended treatment for those with SAD due to its proven therapeutic effectiveness [71]. Bright light exposure is one of the mainstay treatments for seasonal affective disorder [SAD] and severe depression. It is unclear what biological mechanism strengthens the beneficial effects of bright light exposure, despite the fact that this effective treatment has been utilized for decades. The optimal wavelength of light for therapy is also a matter of debate. While the traditional approach uses full-spectrum light, several studies suggest that the key wavelengths are in the blue or green light spectrum. Melanopsin-containing intrinsically photosensitive retinal ganglion cells (ipRGCs) are thought to be the mechanism of action of light therapy. These photoreceptors were shown to be highly sensitive to blue light wavelengths (460 and 484 nm), which are crucial for regulating biological clocks. If ipRGCs are the therapeutic target of light treatment, then it is acceptable to propose that the effects of blue light administration will be similar to those of high illuminance wide-spectrum light [72].

Diabetic Wound Healing: PBM, formerly known as low-level laser (or light) therapy (LLLT), is a non-invasive, non-thermal treatment technique that involves exposing living cells and tissue to light at particular wavelengths. Light-emitting diodes, or LEDs, and lasers are typically employed. Numerous photochemical and photophysical activities are triggered when the photon energy is absorbed by the cells. The electromagnetic spectrum wavelengths known as "light" are UVC (200–280 nm), UVB (280–320 nm), UVA (320–400 nm), visible (400–750 nm), near infrared (NIR, 750–1200 nm), and mid/far IR (1200–10,000 nm) (73).Recent studies indicate that blue light (400–500 nm) and other visible spectrum wavelengths may be beneficial in addition to the advantages of red and near-infrared wavelengths. According to studies, light may effectively destroy bacteria (including Gram-positive, Gram-negative, and mycobacteria), viruses (including DNA and RNA), fungus (including filamentous fungi and yeasts), and parasites. Furthermore, the bacteria's resistance to antibiotics does not seem to affect the antimicrobial's effectiveness, nor does it produce resistant germs after repeated sub-lethal light treatments [73]. While blue light has been found to have a stronger antibacterial effect, red or near-infrared light radiation promotes tissue regeneration [74]. This could be helpful in the fight against infected diabetic wounds [75].

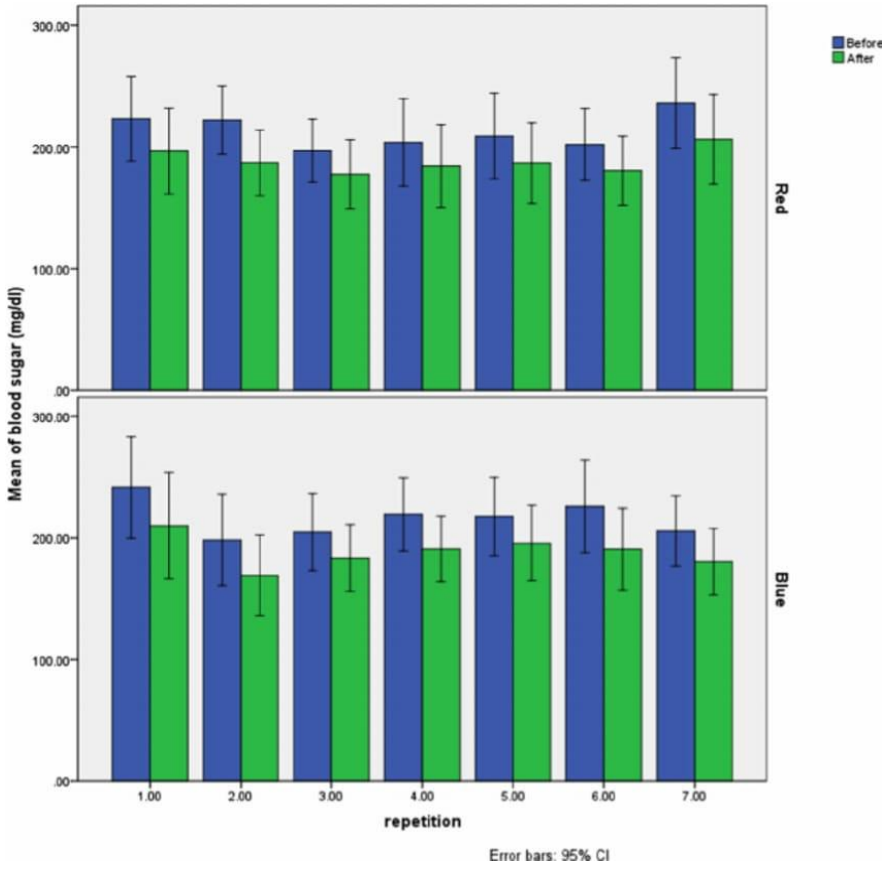

Figure 5: The mean of blood sugar (mg/dl) before and after red/blue laser treatments in seven repetitions [76].

Advantages:

- By exposing only, the damaged areas and protecting the unaffected ones, the risk of both acute side effects like erythema and long-term skin cancer is decreased [77].
- The treatment can only be administered twice or even once a week, and each session minutes short [78].
- Because delivery device is portable and the focused phototherapy equipment requires less space, children can administer it with ease [77].
- PDT is used as a radical or palliative treatment for a variety of cancers and has strong disease specificity and little side effects when compared to conventional and alternative oncological treatments like radiation therapy, chemotherapy, or surgery [79].

Disadvantage:

- They are more expensive, which is a distinct disadvantage [77].
- They are not enough to treat huge areas given the time and cost of treatment. Lesions should not be used if they encompass more than 10% of the body [77].
- Vitamin D deficiency is a sign of photosensitivity [79].
- Eliminating malignant (disease/cancer) cells is the main goal of PDT. PDT influence is also seen in the cells that surround the tumor. Only a few verified studies show that PDT affects healthy cells as well. However, it is undeniable that evaluating normal cells after photoreaction might contribute to a better understanding of the PDT mechanism and principle [79].

CONCLUSION:

In recent years, there has been a lot of interest in the benefits of using laser light as a therapeutic approach for many medical issues, including wound treatment techniques. There have been reports of a variety of biological effects after exposure to light, albeit these are still up for debate. Although

the exact mechanism of action for blue light-induced cytotoxicity is yet unknown, general mechanisms of light–cell interactions are understood. Research on the effects of HEVL in normal cells has garnered a lot of attention when attempting to understand the effects of prolonged, low-intensity exposure to blue light in relation to electronic device screens, curing dental materials, or the treatment of normal retinal, oral, and skin cells. It's possible that endogenous chromophores work similarly to a photodynamic therapy (PDT) agent in healthy cells.

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