Red light irradiation as an intervention for myopia

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Myopia is one of the main causes of visual impairment worldwide.[¹] The prevalence of myopia has been increasing annually as electronic products become widely prevalent. A retrospective meta-analysis showed that the percentages of the world’s population suffering from myopia and high myopia as of 2000 were 23% and 2.7%, respectively.[²] Further, it is predicted that the prevalence of myopia will increase to nearly 50% by 2050, thereby affecting 4.8 billion people worldwide.[³] Therefore, preventing and controlling myopia are of paramount importance. At present, recognized interventions for myopia include administering atropine at low concentrations,[³] orthokeratology (OK) using lenses,[⁴] using defocus incorporated multiple segment (DIMIS) spectacle lenses,[³] and other less popular methods for controlling myopia. Their efficiency for myopia control ranges from 30% to 60%.[⁵] Although these methods can delay the onset and exacerbation of myopia, they are not strong enough to curb the growth of the eye axis. However, recent studies have found that red light irradiation can induce hyperopia and may be effective in suspending myopia progression.[⁶] The role of red light irradiation in the prevention and disruption of myopia progression may be informed more comprehensively through a thorough literature review.

Red light refers to visible light waves with a wavelength of 600–700 nm. Red light has been widely used in clinical settings to treat a variety of diseases, including those in dermatologic, orthopedic, obstetric, and gynecologic settings, due to its strong effects on mitochondrial function. Retinal photoreceptor cells in the eye are rich in mitochondrial structures. In recent years, red light irradiation has been developed as a new application for myopia intervention. Herein, we thoroughly review the application of red light for the reduction of myopia.

Animal Experiments

Animal experiments conducted in the last decade have indicated that red light irradiation can produce hyperopia. For example, Smith et al.[⁸] studied the effects of long-wavelength (red) light irradiation on infant rhesus monkeys. The animals were housed under typical laboratory lighting levels (average = 580 human lux), while the experimental red filters transmitted only wavelengths longer than 570 nm. The transmission increased rapidly for longer wavelengths, with at least 50% of the light transmitted for wavelengths longer than approximately 660 nm. After rearing the animals with long-wavelength-pass (red) filters in front of one or both eyes, the infant rhesus monkeys developed a higher prevalence of hyperopia upon long-wavelength light treatment, compared to the control group. Relative hyperopia is associated with a shorter vitreous cavity. After removing the filter, the monkeys recovered from the induced hyperopia. Studies suggest that reductions in potential chroma cues may interfere with emmetropia and that an environment dominated by long wavelengths may promote the development of hyperopia in infant primate animals.[⁹] Subsequently, Gawne et al.[⁷] studied juvenile and adolescent tree shrews treated with narrow-band long-wavelength (red) light, which almost exclusively stimulated long-wavelength sensitive cones, slowing axial elongation and producing hyperopia. During the

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Received: 03-Jan-2022  Revision: 05-Apr-2022
Accepted: 09-May-2022  Published: 26-Aug-2022

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treatment, long-wavelength (red, 628 ± 10 nm) LED lights were illuminated with either the flickering or steady style, for 14 h per day (10 h of darkness). The mean luminance of the steady red light was 527 lux and 329 lux for the flickering red light, which were measured in human lux using a LX1330B digital illuminance meter (Higadget, Inc.). The results showed that red light induced slowed growth and hyperopia in the juvenile and adolescent tree shrews, demonstrating that long wavelengths may be effective at both juvenile and adolescent ages. Similarly, Ward et al. studied the effects of different red light durations on infant tree shrews. The peak wavelength of narrow-band ambient red light was either 624 ± 10 nm or 636 ± 10 nm, with half peak intensity bandwidth, produced by LED light (American Superlite, San Fernando). The LED light were placed on top of the cage. The mean illuminance of the light ranged from 527 to 749 human lux at the cage floor, while it was approximately 40% greater on the shelf. The infant tree shrews received 13 days of daily narrow-band red light treatment for 0, 1, 2, 4, 7, or 14 h durations. Following each daily red light treatment period, colony lighting was resumed. Compared with the control group, the average degree of hyperopia in the red light irradiation group increased exponentially with treatment duration; the vitreous cavity depth decreased nonlinearly. In short, red light can produce hyperopia in young tree shrews. These findings bring hope with regard to myopia treatment in humans.

Clinical Studies

In addition to animal experiments demonstrating that red light irradiation can produce hyperopia, a few clinical studies have also shown that low-intensity red light laser therapy is effective in controlling myopia. Through a prospective randomized controlled study, Xiong et al. compared the abilities of OK lenses and red light irradiation in terms of myopia control, using low-level laser therapy (LLLT). The wavelength and power of the red light were 650 nm and 2 ± 0.5 mW, respectively, and the beams were produced by a low-level laser device (Ya Kun Optoelectronic Co., Ltd., Wuhan, China). Children in the LLLT group are required to keep their eyes on the red light for three minutes per session, two sessions per day, with at least a four-hour interval between sessions. After six months of follow-up observation, the authors found that axial elongation was slowed, the choroid was thicker in both OK lens-wearers and LLLT-treated children, and red light irradiation treatment led to improved myopia control compared to overnight OK lens wearing.

Mechanistic Hypotheses

Visual development is inseparable from normal optical signal stimulation, and a good visual environment is especially important for refractive development. Single red light exposure differs from a daily wide spectrum sunlight environment. It is of interest that the effect of single red light exposure on refraction cannot be explained by the classical emmetropization feedback theory. [11-13]

An emmetropization feedback mechanism uses defocus visual cues to adjust the axial growth of the eye towards the focal plane. The eye can detect the sign of the defocus (hyperopia, too short; myopia, too long) and modulate its growth in order to achieve and maintain a refractive state of emmetropization. Red light comprises a long-wavelength light wave that is used to create a focus behind the retina within emmetropic eyes. According to the classical emmetropization feedback theory, when the light focuses behind the retina, the eye should theoretically grow towards the direction of the light focus, leading to a longer eye axis and development towards myopia refraction. However, animal experiments and clinical data show that the axial length of mammalian eyes does not increase under red light irradiation; on the contrary, the axial length becomes short and develops towards hyperopia. This is inconsistent with the classical emmetropization theory.

Since the mechanisms mediating red light irradiation–induced hyperopia are unclear, it is necessary to seek a breakthrough based on a knowledge of the physiological structure of the retina. In the retina, visual opsins are located in the outer segments of the rod and cone photoreceptors. Different visual opsins present with specific wavelength ranges for maximal absorption. [14,15] For example, most mammals have two or three opsins, including a short wavelength sensitive opsin (S-opsin), with absorption peaks ranging from ultraviolet to violet light, and a middle/long wavelength sensitive opsin (M/L-opsin). M-opsin is sensitive to middle wavelengths, with max values of approximately 530 nm, and L-opsin is sensitive to long wavelengths, with max values of approximately 560 nm. [16,17] Additionally, Sajdak et al. found that S-opsin was embedded around L-opsin, upon immunofluorescence analysis of the tree shrew retina. Based on the above information regarding the physiological structure of the retina, short wavelength sensitivity (SWS) tends to sense short-wavelength light waves, whereas long wavelength sensitivity (LWS) tends to sense long-wavelength light waves.

Combined with the results of animal experiments, Gawne et al. proposed a new optical model in which the imbalance between SWS and LWS statistical images guides eye growth to the point where the images are statistically balanced. For example, under spectral broadband (“white”) illumination, the focus of the eye is driven to the target point in the middle of the visible spectrum, (i.e., the definition of emmetropia). [20] Under red light irradiation, LWS is over-activated and SWS is not activated, which leads the eye to develop in the direction of hyperopia. [19] On the contrary, under blue light irradiation, although narrow-band blue light stimulates short-wave and long-wave sensitive cones simultaneously, the short-wave sensitive cones are more strongly activated, resulting in failure to maintain emmetropia as well as development towards myopia. [21] In other words, besides the classical defocusing signal, wavelengths of light comprise another optical signal for regulating axial growth.

Effects of Red Light on Ocular Tissues

Animal experiments have shown that red light irradiation can produce hyperopia. Clinical studies have also shown that red light irradiation can effectively prevent and control myopia. Thus, we speculate that red light irradiation will have broad application in myopia prevention and treatment worldwide. However, researchers and physicians should first ensure that red light has no obvious ocular side effects. Herein, we summarize the experimental research with respect to the effects of red light irradiation on the cornea and retina.

Protective Effects on the Cornea

Cell experiments demonstrate that red light has a clear protective effect on the cornea, which can counteract the potential environmental damage of blue light with respect to cell tissue and can reduce mechanical damage to the corneal endothelium.
induced by high intraocular pressure (IOP). Nunez-Alvarez et al.\textsuperscript{[22]} found that low-intensity short-wave blue light reduces the proliferation rates of corneal epithelial cells (hCE-2) in a dose-dependent manner, leading to cell death at a high intensity, whereas high-intensity red light increases the proliferation rate of hCE-2 cells and statistically significantly reduces the negative effects of blue light on cell survival. The toxic effects of blue light on hCE-2 cells involve mitochondrial dysfunction and the activation of apoptosis inducing factor (AIF), p53 mitogen-activated protein kinase (MAPK), and heme oxygenase-1 (HO-1).

Red light can thus prevent the effects of blue light and enhance mitochondrial function. Additionally, the toxicity of sodium azide to cultured hCE-2 cells was demonstrated to be weakened by red light.\textsuperscript{[22]} Moreover, the damage to endothelial cells was statistically significantly reduced by elevated IOP during red light irradiation, compared to complete darkness. Staining the endothelium with JC-1 dye demonstrated that mitochondria are activated by both elevated IOP and red light; however, mitochondrial activation lasted longer for red light. These results suggest that red light can activate mitochondria-induced protective mechanisms to counteract the negative effects of elevated IOP on endothelial cells. At the same time, red light stimulates mitochondrial cytchrome oxidase IV (COX IV), which weakens in situ and in vitro damage to corneal endothelial cells, thereby enhancing cell survival mechanisms.\textsuperscript{[23]} Therefore, we conclude that red light irradiation has a protective effect on corneal tissue.

### Protective Effects on the Retina

Cell experiments have demonstrated the protective effects of red light on the retina. First, red light can counteract the potential environmental damage caused by blue light and/or continuous strong light in retinal cells. Nunez-Alvarez et al.\textsuperscript{[22]} found that short-wavelength blue light has a negative impact on mitochondrial function and tight junctions between cells, leading to oxidative stress and reducing the survival rate for retinal cells. In contrast, long-wavelength red light enhances mitochondrial function, thereby increasing the survival rate for retinal cells and reducing the effects of blue light. Additionally, Albarracin et al.\textsuperscript{[24]} pre-treated adult Sprague Dawley albino rats with red light, after which the researchers exposed the rats to bright continuous light for 24 h. The researchers found that the red light pre-treatment significantly improved expression changes for Müller cell–specific light-induced markers and regulated the role of Müller cells in maintaining retinal homeostasis, promoting neuroprotective effects on the retina.\textsuperscript{[26]} Therefore, the current state of the literature supports that red light can be used as a non-invasive treatment to reduce retinal light damage caused by blue light as well as other strong light sources.

Second, red light can reduce damage to the retina induced by high IOP. Animal studies have shown that a local ischemia model induced by high IOP can reduce levels and counts for glial fibrillary acidic protein (GFAP), calreticulin, calcium-binding protein, choline acetyltransferase, and ganglion cells. Red light irradiation can likewise reduce the negative effects on the rat retina caused by ischemia. Therefore, red light irradiation may also be a potential treatment for glaucoma.\textsuperscript{[27]}

Additionally, red light irradiation can inhibit oxidative stress and cell death induced by diabetes. For example, Tang et al.\textsuperscript{[28]} studied the therapeutic effects of 670 nm photobiomodulation (PBM) on diabetic retinopathy in rodents as well as in cultured cell models. The results showed that 670 nm PBM significantly inhibited the death of retinal ganglion cells caused by diabetes while improving electroretinogram (ERG) amplitude. In vitro cell experiments also demonstrated that PBM inhibited diabetes-induced superoxide generation, retained manganese superoxide dismutase (MnSOD) expression in vitro, inhibited leukocyte arrest and intercellular adherence molecule-1 (ICAM-1) expression, and reduced oxidative stress and cell death. Therefore, we conclude that red light irradiation is a potential treatment for various retinal diseases.

### Side Effects on Ocular Tissues

Although red light irradiation has a hyperopia shift effect on experimental animals and humans, it is important to note the following probable side effects. First, there may be a rebounding effect with further use of red light irradiation. Ward et al.\textsuperscript{[10]} reported that hyperopia refractions in colony lighting returned toward normal after red treatment was discontinued, and the initial rate was linearly related to the amount of hyperopia. Second, red light might damage visual function. In a one-year multicenter, randomized controlled trial of red light therapy in myopia control in children, Jiang et al.\textsuperscript{[29]} did not observe severe adverse events, including sudden vision loss by two lines or scotoma. Moreover, no child was reported to experience glare, flash blindness, or after images following treatment, and according to available OCT data, no structural damage was seen on the photosensory layer. Further, two participants complained about the excessive brightness of the red light and discontinued treatment. Three participants (2.7%) did not achieve 20/20 BCVA at the 12-month follow-up but their BCVA was at 20/25, while it was 8/112 (7.1%) in the control arm. Since presently, the longest clinical study was performed for only 1 year, we cannot infer that there is no visual damage with long-term use of red light therapy. More studies are required and more attention should be given to this issue.

### Conclusion

Based on a thorough review of the literature, we conclude that red light irradiation can produce hyperopia, resulting in myopia prevention and control. Therefore, red light irradiation may be a powerful tool for myopia prevention and control in the future. At the same time, red light has a protective effect on the cornea and retina at the cellular level, suggesting that red light irradiation may be a safe and effective treatment for delaying myopia. Therefore, red light irradiation is expected to play an important role in this regard. However, more studies are needed to enhance the current state of knowledge and inform medical guidelines more comprehensively.

### Financial Support and Sponsorship

This study is supported by Science and Technology program of Jinhua Science and Technology Bureau (Grant No. 2020-4-106) and clinical research program of The First Affiliated Hospital, College of Medicine, Zhejiang University (Grant No. 2022-29).

### Conflicts of Interest

There are no conflicts of interest.

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