· Review Article ·

Photobiomodulation in ocular therapy: current status and future perspectives

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Abstract
● Photobiomodulation has been known to have potential medicinal effects for ages. It involves the use of specific wavelengths to target specific regions in the cell. Different health conditions have been reported to be treated with exposure to light such as cardiovascular conditions, inflammatory diseases, infectious diseases, and most importantly ocular diseases. This review specifically targets the treatment of retinal diseases including age-related macular degeneration, diabetic macular edema, myopia and acute retinal light injury with photobiomodulation. Red light is used in this therapy since this wavelength has lower frequency and hence minimal chance of causing any damage. Red light has the potential to penetrate cellular structures such as mitochondria and facilitate cellular processes. For ocular diseases, the target wavelength ranges between 630 to 800 nm. In most of the cases the primary target for red light is the cytochrome C oxidase enzyme in mitochondria, which alters the gene expression and promotes cellular energy production. Clinical evidence shows improvement of visual activity and reduction in thickness of retina post treatment. Future prospects of photobiomodulation involve target-specific treatment, combinational therapy to treat complex retinal diseases including gene therapy, and longitudinal studies to predict long-term efficacy and the chance of any recurrence in the patients. Hence the future of photobiomodulation holds significant potential in medicine especially in ocular diseases characterized by progress in research, technology, and clinical trials.
● **KEYWORDS:** photobiomodulation; retina; near-infrared; ocular diseases; light therapy

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INTRODUCTION

Light therapy has been known to have therapeutic effects for a long time. This phototherapy involves the application of sunlight or artificially generated light of certain specific wavelengths aimed at the targeted region of the body. Phototherapy has been proven to treat various health conditions including inflammatory diseases, infectious diseases, and diseases related to optics and seasonal affective disorders[1]. Among light wavelengths, red light is most prominent concerning therapeutic applications and has been implemented since contemporary times with the title of low-level laser energy or photobiomodulation (PBM). Red light is composed of longer wavelengths and lesser frequency[2]. The specific wavelengths utilized in photobiomodulation are far-red to infrared. Either a laser or light emitting diode is used to omit the wave rays of wavelength around 600 to 1000 nm. Due to the larger wavelength, these waves can penetrate the body tissues. Current applications of the PBM system involve facilitation in wound healing by repairing the damaged tissue, improvements in cardiac conditions, improvement in neurological pains, and nerve repair after injury[3].

PBM has a wide range of applications in the field of ophthalmology. Wavelength suitable for optical operations falls under the range of visible to near-infrared region. Typically employed wavelengths for the retina include 630 nm from red light area and 850 nm from near-infrared region[4]. However, the value of wavelength may vary depending on the therapeutic effect desired. For example, a wavelength 600-700 nm is specific and effective in targeting superficial layers within the retina, while on the other side, a higher wavelength of around 800 to 900 nm can deeper penetrate within the eye tissues. The targeted function of light in the retina is to promote the cellular processes in beneficial ways in retinal disease conditions such as retinitis pigmentosa, age-related macular degeneration, and diabetic retinopathy[5].

Different cellular processes are targeted by the light at specific wavelengths. For PBM of the retina, red to near infrared (NIR), the targeted region is mitochondrial proteins specifically cytochrome C oxidase (CcO). A cascade of events is initiated by the activation of CcO. Activated CcO increases the bioproduction of energy reservoir adenosine triphosphate (ATP)[6]. It also promotes the downregulation of harmful oxidative species from the cell and promotes antioxidant stability. As a result, the cellular processes are restored to normal. Restoration is observed in different forms such as regulating gene expression, calcium signaling, and activating transcriptional factors[7]. Moreover, different pathways associated with cell death and inflammatory reaction are also regulated as illustrated in Figure 1.

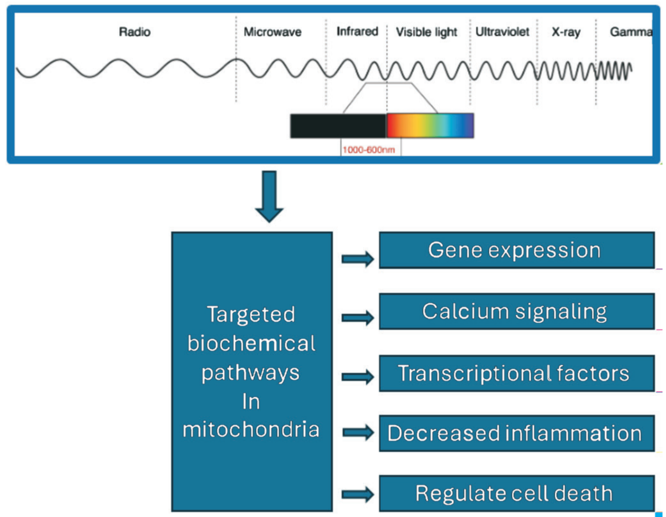

Figure 1 Impact of red light on molecular ad signaling pathways in mitochondria.

The human eye is designed to capture light through receptors and convert light energy into electrical signals which are being executed by the brain to form images. The organ responsible for this transformation is the retina. The first step in phototransduction is carried out by photoreceptors in the retina which convert specific wavelengths into neural signals[8]. Light striking initiates a series of biochemical reactions involving multiple enzymes and coenzymes within the mitochondria of cells in the retina which initiate nerve signals in the brain. Signals from rods and cones of the eye are processed by different types of neurons in the brain and are expressed in the form of action potential in the ganglia of those retinal cells whose axons are associated with the formation of the optic nerve[9]. Since the retina is entirely dependent upon the precise supply of light energy and any alteration in the supply of energy is related to the mitochondrial damage, hence retina appears to be a potential therapeutic target for photo biomodulation[10].

Research has been carried out to find the therapeutic impact of PBM in optical diseases and preclinical studies have shown that PBM therapy has the potential to hinder cell death, reduce the number of reactive oxygen species and reactive nitrogen species, and promote the balanced immune responses in retinal cells against any physical or biochemical damage[11]. An *in vivo* study results showed the PBM is effective in reducing oxidative stress, hyperoxic stress, age-related alterations, and retinopathy in the retina. At the molecular level, genes and proteins involved in producing inflammatory responses are modulated and as a result, there is a decrease in the production of mediators like C2a nd C3a[12].

HISTORY

The therapeutic effect of PBM is attributed to Ender Mester, who is considered as the father of PBM. In his experiment in 1967, he used low-level red waves to treat tumor cells in rat models. Although he could not find any progress in tumor treatment, he observed increased hair growth and more specifically the regrowth of hair in the targeted area imposed by the exposure of light rays[13]. The potential of PBM sparked interest and certain other experiments were also conducted in which red light was shown to heal various wounded areas. It is not wrong to say that red light stood promising therapeutic benefits in history. Certain other notable milestones of red light in history involve the work of Finsen in the 18th century. Niels Fensen utilized red light with longer wavelengths to treat certain skin conditions[14]. He cured small blisters present on the skin by targeting them with red and near-infrared wavelengths. He also treated lupus vulgaris by targeting the lesions with ultraviolet radiation. These therapeutic findings were a big milestone pointing towards the potential of red light in medicine and hence he is termed the "Father of Contemporary phototherapy" and also won the Nobel Prize in 1903[15].

With the passage of time and advancements in scientific research, more therapeutic aspects have been discovered about PBM. The therapeutic aspects are diverse, ranging from one type of treatment to another in another part of the body. Such effects have been observed by *in vivo* studies conducted in animal models as well as in clinical studies involving disease patients. The range of therapeutic effects involve wound healing, alleviating pain, cognition, cancer as well as diabetes[16]. It also heals and accelerates the recovery phase of tissues post injury such as peripheral tissues and retinal tissues and in worse cases, it helps to better alleviate traumatic brain injury. Other than above mentioned therapeutic aspects, there are many retinal approaches as well which are discussed in this literature review. Few of the highlighted retinal conditions include diabetic retinopathy, amblyopia, age related macular degeneration[17].

MECHANISM OF ACTION

The mechanism of action of PBM is entirely different from

Table 1 List of therapeutic impacts of photobiomodulation on different organs of body

Serial No.	Factors	Effect	Model	References
1	Toxic effect of formic acid in mitochondria of retina	Inhibit working of CcO	Rat models	Absorption measurements of a cell monolayer relevant to phototherapy: reduction of CcO under near IR radiation[21].
2	Exposure to red light stimulates CcO production	Increased metabolism, increases cell proliferation,		Therapeutic photobiomodulation for methanol-induced retinal toxicity[22].
3	Effect of photobiomodulation in diabetic rats	Reduction of inflammation induced by diabetes, reduced retinal vasculature	Rat models	Low-intensity far-red light inhibits early lesions that contribute to diabetic retinopathy: *in vivo* and *in vitro*[23].
4	Effect of photobiomodulation on fibroblast cells through cDNA microarray analysis	Altered gene expression, upregulation of mitochondrial respiratory chain proteins, upregulation of antioxidant genes.	Cell cultures	cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light[24].
5	Effect of photobiomodulation on gene expression.	Downregulation of apoptotic genes, downregulation of stress genes.		Enhancement of nitric oxide release from nitrosyl hemoglobin and nitrosyl myoglobin by red/near IR: potential role in cardioprotection[25].

CcO: Cytochrome C oxidase; IR: Infrared.

the previous conventional laser techniques. Earlier techniques primarily relied upon thermal mechanisms of either heating or cooling to treat certain medical conditions such as tissue ablation, coagulation, photocoagulation, and skin healing. However, some of the side effects are associated with the excessive use of thermal-based laser techniques such as pain and discomfort during the treatment, partial and temporary redness in the target area, and bruises and infection in rare cases[18]. PBM uses red light of wavelength range between 630 to 1000 nm with low intensity to treat the targeted area. During the late 1980's and 1990's scientists already started identifying the mechanism of action of laser light upon cells and indicated that main target within cellular structures is mitochondria. CcO is a large transmembrane protein complex and functions as the primary acceptor of light energy into the mitochondrial compartment[19].

CcO plays an integral role in the electron transport chain of energy production in mitochondria. The enzyme assists in the shift of electrons from cytochrome to the end acceptor *i.e.*, molecular oxygen. Research in this field suggested that CcO is the primary mediator of electron transport chain and vital photoreceptor as maximum efficiency was observed in this region in action spectrum (Figure 2).

Different tests conducted with cell cultures of primary neurons, HeLa cells and animal models of rat emphasize the importance of CcO for PBM. As the cells were exposed to red light with wavelength around 670 nm, they inhibit the production of tetrodotoxin and increases the production of CcO. The reason is that since tetrodotoxin acts in such a way to block production of CcO, a decreased level of it will automatically upregulate CcO in primary neuron cells[20]. A list of therapeutic impacts of PBM on retina and other organs is demonstrated in Table 1[21-25].

There has been evidence regarding the impact of PBM on the availability of nitric oxide (NO) in the cells. Research suggests that PBM treatment enhances the amount of NO by releasing nitrogen from heme-containing proteins. In a study conducted on HeLa cell cultures, it was found that PBM

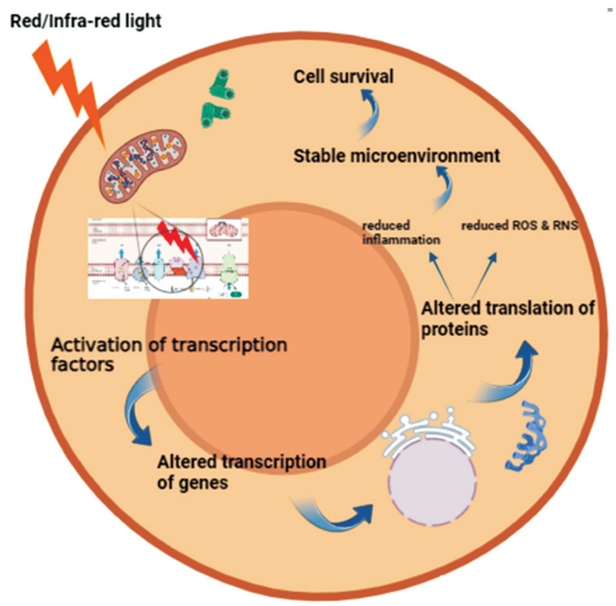

Figure 2 Mechanism of action of red/near-red light on cellular processes.

assists in enhanced respiration and energy production process by removing the NO from the cytochrome C complex, since NO is an inhibitor of CcO. Overall energy production and metabolism is promoted. Along with the positive influence of PBM at gene expression and enhanced cellular activity and energy production, it also promotes neighboring retinal cells to exhibit an intrinsic effect. For example, the Müller cells in retina are promoted to provide protection to the photoreceptors and provide an overall favorable effect[26].

Not all wavelengths of light are protective. Light with shorter wavelengths such as the blue light can induce damage in eyes especially retinal cells. A study was conducted with rat models of light-induced retinal degeneration. The study aimed to evaluate the impact of longer wavelength light rays on retinal recovery. The light waves were used at the wavelength of 670 nm. Treatment has a clear positive effect on the Müller cells in the retina. A few of the obvious beneficial changes in Müller cells reported were increased preservation of cellular structures, a clear decrease in stress and elimination of gliosis. Another important finding of the study showed there was

Table 2 List of clinical studies involving photobiomodulation therapy for age-related macular degeneration

Serial No.	Title	Author	participants	Device	Year	Reference
1	Treatment with 670 nm light up regulates cytochrome C oxidase expression and reduces inflammation in an age-related macular degeneration model.	Begum	*In vivo* study; mice model; *n*=29	LED light source	2013	[30]
2	670 nm LED ameliorates inflammation in the CFH(-/-) mouse neural retina.	Kokkinopoulos	*In vivo* study; mice models; *n*=46	WARP10 LED Device	2013	[31]
3	Low-level laser therapy improves vision in patients with age-related macular degeneration.	Ivandic	*In vivo* clinical study; human participants; *n*=203	Custom device	2008	[32]
4	Photobiomodulation as a new treatment for dry age-related macular degeneration RESULTS from the Toronto and Oak Ridge Photobimodulation study in AMD	Merry	*In vivo* clinical study; human participants; *n*=9	WARP10 LED Device	2019	[33]
5	A double-masked, randomized, sham-controlled, single-centre study with photobiomodulation for the treatment of dry age-related macular degeneration.	Markowitz	*In vivo* clinical study; human participants; *n*=30	Valeda Light Delivery System	2020	[34]

LED: Light emitting diode; AMD: Age-related macular degeneration; CFH: Complement factor H.

a balanced metabolic state of Müller cells since glutamine synthetase was continuously being produced by the cells. In addition to this, Müller cells are a key component in reducing the inflammatory changes in the cells. Inflammation leads to the immune responses by the cells which triggers the disease progression. Decreasing inflammation provides a solution to hinder disease progression. Another important aspect with respect to the Müller cells is these cells are involved in reduced activation of NO and pretreatment with PBM at 670nm is helpful in downregulating the tumor necrosis factor (TNF) production which in turn reduces the production of NO enzyme and ultimately an overall decrease in reactive NO species[27].

PHOTOBIOMODULATION IN OCULAR DISEASES

Age-Related Macular Degeneration Age related macular degeneration is an eye disease associated with blurriness in eyes associated with age progression. Macula in eye is responsible for clear vision and with time, it is damaged. Different clinical studies have been carried out with PBM to improve the functioning of macula. In patients with age related macular degeneration, light therapy with longer wavelength falling within the range from 600 to 750 nm, there was a significant improvement in visual acuity[28]. Disease progression also slowed down. A few of the studies employing clinical cases of PBM of age-related macular degeneration are enlisted in Table 2. However, the first ever study employing light of a larger wavelength was carried out in 2008 with a semiconductor laser diode. As a result of this approach, there was a clear visual acuity. Disease symptoms of age-related macular degeneration were also decreased such as decreased retinal bleeding, drusen, and decreased pigment accumulation. The study did not show any of the side effect of both physical and morphological nature. The study proved to be strong evidence in support of the therapeutic potential of PBM for treatment of both early and advanced age-related macular degeneration. It also suggests the importance of this technique as a side effect free technique[29]. A list of a few of the completed and ongoing clinical studies involving PBM for treating age related macular degeneration are mentioned in Table 2[30-34].

Diabetic Macular Edema Diabetic macular edema is caused in diabetic patients due to uncontrolled sugar levels. It results in excessive accumulation of fluid in the extracellular space of the retina specifically in the macular area. Blood vessels are damaged due to which blood-retina barrier is damaged and increased blood flow occurs in the macula. As a result of which it causes impaired vision[35]. PBM is the significant approach to targeting oxidative stress and inflammatory responses in retina of the eye. A research study revealed that when retinal macular cells are exposed to low wavelength energy waves of 670 nm for 5wk, there is a considerable decrease in the thickness of foveal post-treatment. Similarly, another study conducted with PBM showed a significant decrease of central retinal thickness and even without causing any side effects[36].

Acute Retinal Light Injury Photoreceptors are designed to receive light energy and transmit the signal further to other organs. However, light waves with shorter wavelengths can be damaging to the eyes and may cause damage or even death of the photoreceptors. As a result, the muller cells are effected as well as the shrinkage of the choroidal vessels[37]. Another study showed that when retinal cells are targeted by the shorter wavelength of 670 nm, falling in the region of red light, it results in the decreased production of inflammation, a decreased level of microglia and macrophage infiltration. It also showed promising results of decreased cell death in photoreceptors. Similarly, another research[38] conducted regarding PBM showed that when retinal cells are targeted with wavelengths of 670 nm and 810 nm, and it showed a remarkable increase in energy production by mitochondria and increased ATP production. Since the mice models used in this study were light induced damage, hence the study showed red light therapy can revert the damage imposed by blue light. PBM can also promote cell metablosim and cellular energy production processes.

Myopia Myopia termed as the issue with seeing far objects clearly arise when the eyeball is too big from front to back. As a result, far objects are not visible to the naked eye. Lenses can be used to treat myopia. But high myopia is associated with an increased risk of complications with retina[39]. Few conditions include retinal detachment and degeneration. Furthermore, in another study, it was observed that exposure to red light greatly reduced the likelihood of infant monkeys developing form deprivation myopia in response to imposed hyperopic defocus[40].

Future Prospects of Photobiomodulation in Treatment of Ocular Diseases With progressive advancements in medicine, PBM is achieving milestones, therapeutic effects of PBM in treating ocular diseases in future are promising. A few of the characteristics that make PBM a successful technique is its non-invasive nature and ability to target specific cellular components such as mitochondria. Being a target specific approach makes it a promising treatment option for retinal diseases. There are still further aspects and exciting and promising applications of PBM in retinal diseases[41]. Currently wavelengths ranging from 670 to 800 nm range are used in treating ocular diseases specifically diseases associated with retinal damage. Future prospects targets at precision wavelength use conditioned with energy doses. In this way specific pathways involved in disease pathology can be targeted and hence side effects could be further reduced. Another important future prospect of PBM is combinational therapy. Combining PBM with other advanced molecular techniques such as gene therapy holds promising results. It can help in targeting multiple specific pathways at the same time. It can help in targeting complex retinal diseases[42].

Currently a lot of clinical studies are available that confirm the efficacy and potential of PBM, and since this technique holds a high place in future research, need of the hour is to carry out clinical trials to found out long term efficacy and safety of PBM. Longitudinal studies are the best approach in this aspect. It can help in identifying any side effects in the long run. Hence it would be possible to detect the chances of disease recurrence at any time in the future. Collectively it is right to say that future of PBM holds significant promises in collaboration with advanced research and technology[43].

CONCLUSION

Overall, the application of PBM appears to be a promising and innovative medical intervention for treating ocular conditions. It possesses the potential to treat a variety of retinal diseases. In this review, the therapeutic potential of light therapy is being discussed, as how a specific wavelength spectrum can penetrate the cell membrane of retinal cells and target specific sub-cellular structures without imposing any potential damage and hence stimulate the cellular energy production and reducing harmful effects such as inflammation and oxidative stress. Since long ago, PBM has been in medicinal practice and a lot of research has been carried out to understand the underlying mechanism of action of red light on retinal cells. It is stated that mitochondria and enzymes of electron transport chain are targeted specifically CcO and it results in overall upregulation of energy production. Processes of calcium signaling gene expression and inflammation are modulated and could be considered as target pathways to bring out further therapeutic potential of PBM. Clinical studies have provided clear evidence for the effectiveness of PBM in treating patients with visual acuity, increased retinal thickness, and other ocular disease symptoms. The potential of PBM ranges from non-invasive and target specific to a technique with minimum side effects. In future, PBM therapy signifies a milestone in medicine in combination with advanced techniques, extensive clinical testing and profound research. In future, PBM will be used as combinational therapy and will be focused at more specifications such as target-specific treatment, combination of personalized medicine with molecular techniques. Furthermore, longitudinal studies should be carried out to find out the chances of any long-term side effects. Further, for availing the future potential of PBM, a collaborative effort among researchers, engineers and clinicians is required to harness full scope of this light therapy. With this collaborative approach, PBM is expected to come up as a milestone for treating ocular diseases and new hopes and possibilities for patients across the globe.

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