Photobiomodulation therapy as a new hope therapy for retinitis pigmentosa: a systematic review

Terapia de fotobiomodulação como nova terapia de esperança para retinite pigmentosa: uma revisão sistemática

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ABSTRACT

Retinitis pigmentosa is one of the leading causes of hereditary blindness in developed countries and unfortunately there is currently no cure. Photobiomodulation therapy can penetrate the retina and optic nerve and restore the function of damaged mitochondria as an intracellular target. This study is proposed to review and analyze photobiomodulation as a strategy that has the potential to be a new hope therapy and non-invasive treatment for retinitis pigmentosa in the long term. PubMed® and Google Scholar were used to perform a systematic review of photobiomodulation as a therapy for retinitis pigmentosa. Using PRISMA 2020 Guidelines, we include seven studies in this review. The inclusion criteria for each study were as follows: the study documented the use of photobiomodulation therapy for retinitis pigmentosa, was conducted in human eyes or animals' eye, its full text was in English, and it published in the last 10 years. We anticipated that most studies would be experimental design, we evaluated the quality of eligible studies using relevant items from the ROBINS-I, which is the recommended tool to evaluate experimental study. There is a clinical improvement in visual acuity and visual fields. Further eye examination showed functional and outer nuclear layer preservation, decline waveforms of electroretinogram slower than control, disruption of retinal pigment epithelium, and preserved photoreceptor nuclei twice thicker than control ($p < 0.05$). Photobiomodulation also increases retinal mitochondrial function and maintains mitochondrial redox state, revealing significant recovery of photoreceptors' cell function. Photobiomodulation showed significant change in clinical improvement, mitochondrial repair, and retinal layer thickening; thus, photobiomodulation can be a new hope for therapeutic strategies for retinitis pigmentosa. Several studies only have a few participants, so it does not provide a long-term outcome in retinitis pigmentosa.

RESUMO

A retinite pigmentosa é uma das principais causas de cegueira hereditária em países desenvolvidos e, infelizmente, não há cura atualmente. A terapia de fotobiomodulação pode penetrar na retina e no nervo óptico e restaurar a função das mitocôndrias danificadas como alvo intracelular. Este estudo propõe-se a rever e a analisar a fotobiomodulação como estratégia que tem potencial para ser uma nova esperança terapêutica e tratamento não invasivo para a retinite pigmentosa a longo prazo. PubMed® e Google Scholar foram usados para realizar uma revisão sistemática da fotobiomodulação como terapia para retinite pigmentosa. Usando as diretrizes PRISMA de 2020, incluímos sete estudos nesta revisão. Os critérios de inclusão para cada estudo foram os seguintes: que tivesse documentado o uso de terapia de fotobiomodulação para retinite pigmentosa; o procedimento tivesse sido realizado em olhos humanos ou olhos de animais, e o texto fosse completo, em inglês, e publicado no último 10 anos. Previmos que a maioria dos estudos seria de desenho experimental, avaliamos a qualidade dos estudos elegíveis usando itens relevantes do ROBINS-I, que é a ferramenta recomendada para avaliação de estudo experimental. Houve melhora clínica da acuidade visual e dos campos visuais. O exame oftalmológico adicional mostrou preservação funcional e da camada nuclear externa; declínio das formas de onda do eletrorretinograma mais lento que o controle; ruptura do epitélio pigmentar da retina e núcleos fotorreceptores preservados duas vezes mais espessos que o controle ($p < 0,05$). A fotobiomodulação também aumenta a função mitocondrial da retina e mantém o estado redox mitocondrial, revelando uma recuperação significativa da função celular dos fotorreceptores. A fotobiomodulação mostrou mudança significativa na melhora clínica, reparo mitocondrial e espessamento da camada retiniana. Assim, a fotobiomodulação pode ser uma nova esperança para estratégias terapêuticas para retinite pigmentosa. Vários estudos têm apenas alguns participantes e, por isso, não fornecem um resultado a longo prazo na retinite pigmentosa.

INTRODUCTION

Retinitis pigmentosa (RP) is a leading cause of inherited blindness in the developed world with a global prevalence of 1:4,000.[1] There is currently no treatment for RP; therapies can only slow the progression.[2]

Photobiomodulation therapy (PBMT), known as low-level laser therapy (LLLT), has lately gained attention as a promising new approach to treating retinal disorders. Several studies have shown that PBMT using far-red (FR) or near-infrared (NIR) spectrum can penetrate the retina and optic nerve.[1,3,4] It has the ability to restore the function of damaged mitochondria as an intracellular target that is primarily the cause of RP.[5,6]

Mitochondrial repair and reduction of oxidative stress are essential for long-term retinal survival. Understanding the mechanisms involved in photoreceptor and retinal degeneration is important for the development of therapeutic strategies to treat these diseases.[1,6] Thus, we conducted a systematic review about PBMT as a therapeutic strategy that can be a promising non-invasive therapy for RP in the long term.

Pathogenesis of retinitis pigmentosa

Retinitis pigmentosa is a group of hereditary disorders characterized by progressive loss of peripheral vision and night vision disorders (night vision) that can lead to loss of central vision.[7]

This degenerative disease of the retina is caused by progressive degeneration of rod photoreceptor cells due to mutations in the MER-proto-oncogen tyrosine kinase (MERTK) gene. MER-proto-oncogen tyrosine kinase is involved in the efficient phagocytosis of shed photoreceptor outer segments (POS) by the retinal pigment epithelium (RPE). As a result of this gene abnormality, phagocytosis is impaired, resulting in the accumulation of shed POS and the subsequent formation of subretinal debris. Ultimately, this mutation causes a gradual loss of photoreceptors.[8,9]

Oxidative damage is usually minimized by the body's own antioxidant and repair system. Aging and retinal disorders increase mitochondrial dysfunction and oxidative damage.[6] Mitochondrial dysfunction and oxidative stress have been demonstrated to play important roles in the pathogenesis of RP.[1]

Photobiomodulation therapy overview

Low-level light therapy in the FR to NIR region of the spectrum (~600-1000 nm),[10]but the injections must be given frequently and usually for years. Here we report laboratory and clinical studies on the safety and efficacy of 670 nm photobiomodulation (PBM) collectively referred to as photobiomodulation (PBM), has recently become a new tool worldwide. It is attracting attention for experimental treatment applications in various medical conditions.[11] Studies have shown that PBM activates mitochondrial signaling pathways via FR / NIR, restores damaged mitochondrial function, increases production of cytoprotective factors, suppresses oxidative stress, and causes cell death. It has been shown to prevents cell death.[11,12]

Cytochrome oxidase (CO) is a major photoreceptor and a key enzyme in oxidative metabolism, so it is especially beneficial to the eye and brain. The effect of PBMT can be the primary effect and the secondary effect.[11]

These effects are light dependent, as the main effects occur during exposure to light. For example, NIR light can promote oxidation by cytochrome c, thereby inducing increased oxygen consumption, increased sensitivity of mitochondrial membranes, and mitochondrial pore permeability. These effects are caused by an increase in the flow of electrons in the mitochondria. Therefore, the main effect depends on the characteristics of the light.[11]

The secondary effects of light occur after exposure to light. These can occur as a result of primary effects, biochemical, and biological reactions that affect cell hemostasis. Light can initiate several signaling pathways from the mitochondrial inner membrane, transmitting signals to activate photoreceptors (cytochrome c) and then translocating to the nucleus to alter gene expression and protein synthesis. These pathways improve energy metabolism and the production of antioxidants.[11]

The overall effect is to improve cell viability. The most important result of these signaling pathways is upregulation of CO activity. CO is the rate-determining step of mitochondrial respiration, improving respiratory efficiency under oxidative stress conditions and thereby suppressing the production of reactive oxygen species.[1,3,11]

METHODS

Study selection

A literature search was carried out on PubMed® and Google Scholar. We searched for studies that evaluate PBMT and RP,

Search strategy

Draft entry PubMed Search

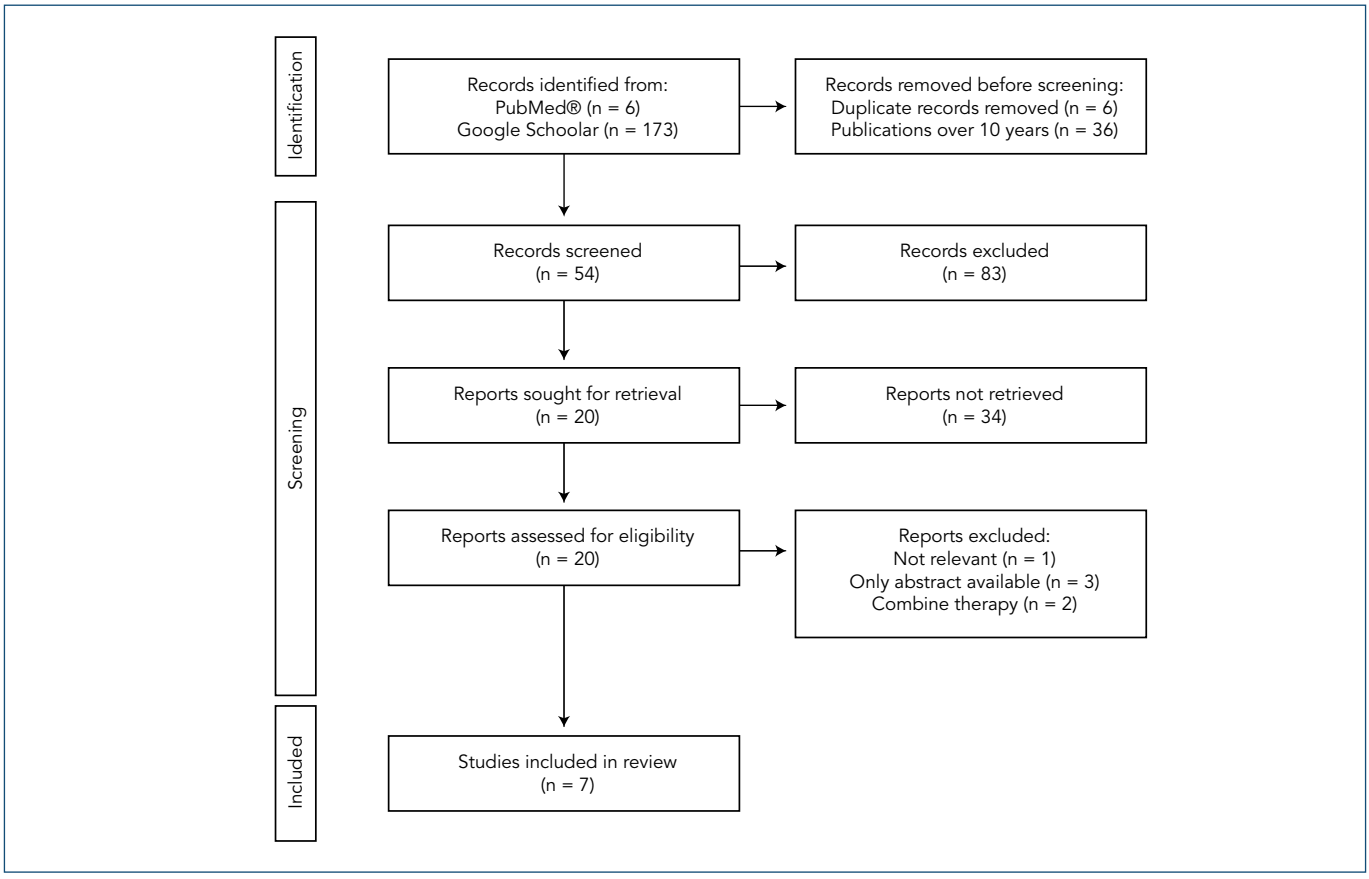


Figure 1. Flow diagram of study selection process.

No	Entry	Filter	Total Findings
1	(((((“phototherapy”[MeSH Terms]) OR (“Low Level Light Therapy”[Text Word])) OR (“Low-Level Laser Therapy”[Text Word])) OR (“Laser Phototherapy”[Text Word])) OR (“Light Therapy”[Text Word])) OR (Photobiomodulation Therapy)	None	5,828
2	((“Retinitis Pigmentosa”[MeSH Terms]) OR (“Retinal Degeneration”[Text Word])) OR (“Retinal Diseases”[Text Word])	None	5,084
3	S1 AND S2	none	234
4	S1 AND S2	Last ten years and full text	61

Draft entry Scholar Search

No	Entry	Filter	Total Findings
1	“low-level light therapy laser” OR therapy “photobiomodulation” AND “Retinitis Pigmentosa”	None	322
2	“low-level light therapy laser” OR therapy “photobiomodulation” AND “Retinitis Pigmentosa”	Last ten years	280

Inclusion criteria

The inclusion criteria for each study were as follows: it documented the use of PBMT for RP, was conducted in human eyes or animals’ eye, the full text was in English, and it was published in the last 10 years. We adhered to the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Figure 1).

Initially, two authors independently screened the titles and abstracts of the identified studies from the database to identify all potentially eligible studies. After rechecking the source data, disagreements in study selection were discussed between the authors, and where consensus could not be reached a third author would be included for final decision making. Full articles that met the inclusion criteria were read; the others were discarded. In addition, reference lists of relevant studies were hand-searched to identify additional studies that met the inclusion criteria.

Study eligibility criteria

The population-intervention-comparator-outcomes-study design (PICOS) framework was used to identify eligible cases, as follows:

- Population: human or animals, with no restrictions on age or other demographics.
- Intervention and comparator: the use of PBMT on RP. We excluded the combinations of therapy. No comparator was required.
- Outcomes: visual acuity improvement, mitochondrial repair, retinal layer thickening.

Table 1. Studies included in this review

First author	Design	Subjects	Eyes (no)	Dose and delivery parameters			Duration	Results
				λ (nm)	power density (mW/cm²)	energy density (J/cm²)		
Gopalakrishnan et al.[1]	Experimental study	P23H rats	N/A	830	25	4,5	Once a day in 15 days (5 days on 2 days off)	Preserves the mitochondrial redox state (higher redox ratio, increasing NADH, decreasing FAD), preserving retinal structure (retinal and ONL thickness), protect photoreceptor cell loss
Kirk et al.[3]	Experimental study	P23H rats	9	670	50	9	Once a day in 5 days for 180 seconds	Increase retinal mitochondrial cytochrome oxidase (in INL and GCL), improve photoreceptors function and reduce photoreceptors cell loss. (TUNEL+ cells in the ONL was reduced 70%), preserve retinal tissue
Kang et al.[8]	Experimental study	Rats	30 rats divided into 6 groups (n=5 per group) Fellow eye as control	N/A	40	N/A	Single dose for 15 ms	FA: hyperreflective spots, indicating disruption of the RPE in laser treated area ERG: Waveforms decline slower with time in treated eye than in control eye B-wave: the laser pattern density of 1.5 d was optimal for functional preservation OCT: ONL preservation in laser-treated eyes until P180 while in control, ONL was not distinguishable after P98 mfERG: preservation of ONL only in the treated central retina, whereas little to no ONL was observed in untreated eye Histology: in treated eye, exhibited the best-preserved photoreceptor layer, up to five rows of photoreceptor nuclei, while in control eye displayed no discernible photoreceptor layer or their nuclei
Lorach et al.[9]	Experimental study	Rats	12 eyes (fellow eyes as control)	577	40	N/A	N/A	mfERG: responses only in the laser-treated area, no response in control OCT: delays the loss of photoreceptors Histology: twice thicker ONL in the laser-treated area ($p < 0.05$) B-wave: amplitudes were higher in the laser-treated eyes than control
Ivandic et al.[13]	Case report	RP patient	2	780	N/A	0,4	2 times per w for 2 weeks (for 40 s each)	Increased visual acuity from 20/50 at baseline to 20/20 in each eye (uncorrected) No adverse effect was noted
Ghanian et al.[12]	Experimental study	P23H rats	12 eyes divided into 3 groups (4 eyes per groups)	670	50	4,5	for 90 sec	Less oxidative stress in mitochondrial respiratory chain (20% increase the NADH RR), which reveals a significant recovery of photoreceptors cell function in retina
				830	25	4,5	for 180 sec	
Gkotsi et al.[14]	Experimental study	rats	79	670	40	N/A	7 times spaced evenly over 84 hours, for 90 seconds	ATP is increased significantly by 670 nm exposure, associated with increased COX and reduced acrolein expression

N/A: not applicable; NADH: Nicotinamide Adenine Dinucleotide; FAD: Flavin Adenine Dinucleotide; ONL: outer nuclear layer; INL: inner nuclear layer; GCL: ganglion cell layer; TUNEL: Tdt-mediated dUTP-biotin nick-end labeling; FA: fluorescein angiography; RPE: retinal pigment epithelium; ERG: electroretinogram; OCT: ocular CT; mfERG: multifocal electroretinogram; RR: Redox Ratio (RR= NADH/NAD); ATP: Adenosine Triphospate; COX: Cytochrome c Oxidase.

- Study design: we included only primary studies or case report, published in full text.

Data collection and risk of bias of individual studies

We extracted data on study characteristics, RP in human or animals, and PBMT in RP. We anticipated that most studies would have experimental designs, we evaluated the quality of eligible studies using relevant items from the ROBINS-I, which is the recommended tool for evaluating experimental study.

Two authors extracted data and evaluated the risk of bias of study. Any disagreement between authors were discussed and where consensus could not be reached a third author would be included for final decision making.

RESULT

Study selection

The literature search across multiple databases identified a total of 179 records from PubMed® (n=6) and Google Scholar (n=173). After discarding duplicates (n=6), removing publications over 10 years (n=36), obviously irrelevant records (n= 83), 13 records remained and were screened in full text. Of these, six were excluded because they did not fulfill our eligibility criteria. Seven records were deemed eligible and included for the review (Figure 1)

Individual studies

Seven studies were included for the review, with 6 experimental studies and 1 case report. All experimental studies used rats or mice, while the case report was conducted in human eyes. The dose and delivery parameters of PBMT was 670, 780 nm, 830 nm, mostly once daily, some for 5 days, some for 15 days. (Table1)

The only one that uses PBMT on human patient is the study by Ivandic et al. The authors reported that there was improvement on patient's visual fields. The patient initially presented with reading difficulties and night blindness, and eye examinations revealed blue-yellow color blindness and 20/50 uncorrected visual acuity in each eye, but no improvement with optical correction. The field of view was reduced to a very narrow central residual of 5 degrees (Figure 2). Fundus examination showed typical patterns of retinal pigment epithelium and narrow retinal blood vessels. After 4 treatments (first 2 weeks), clinical improvement was seen: visual acuity increased

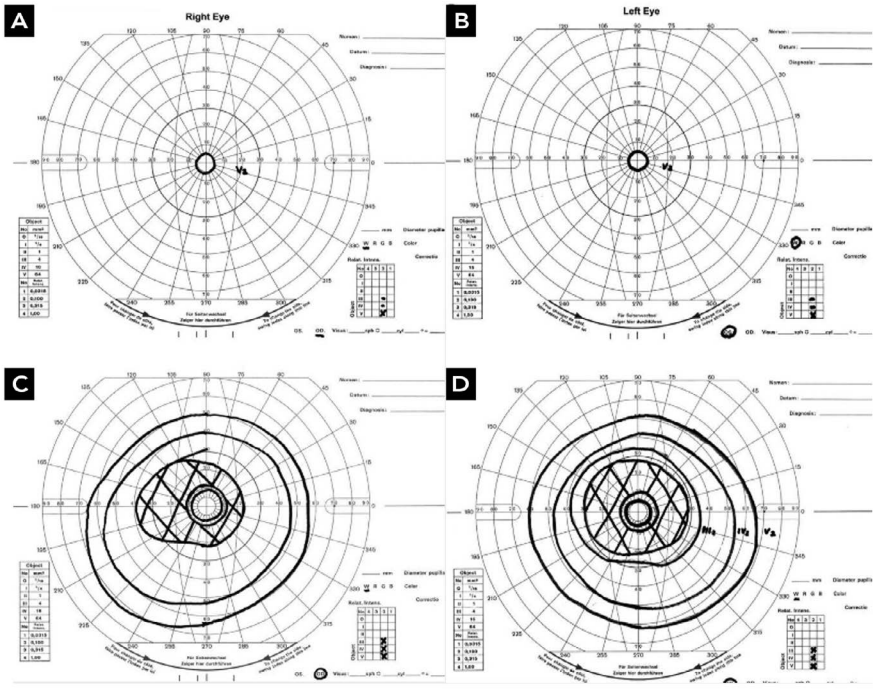


Figure 2. Visual fields were assessed by Goldmann perimetry. Before (A, B) and after photobiomodulation therapy (C,D).[13]

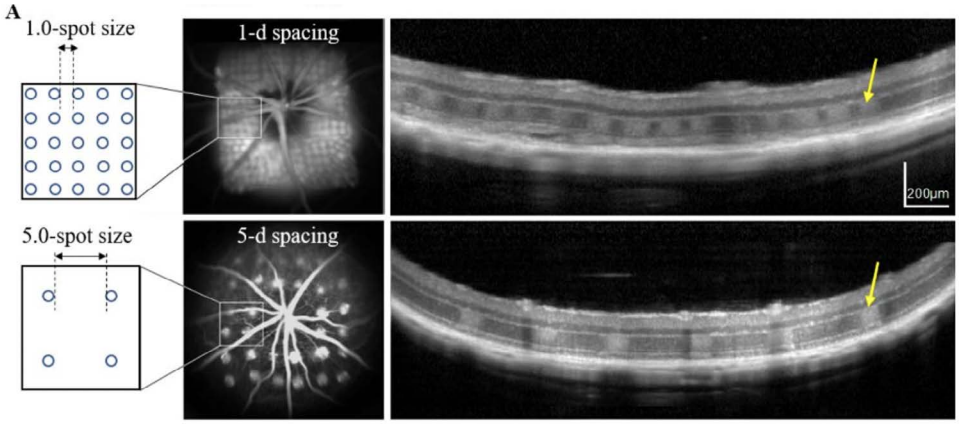
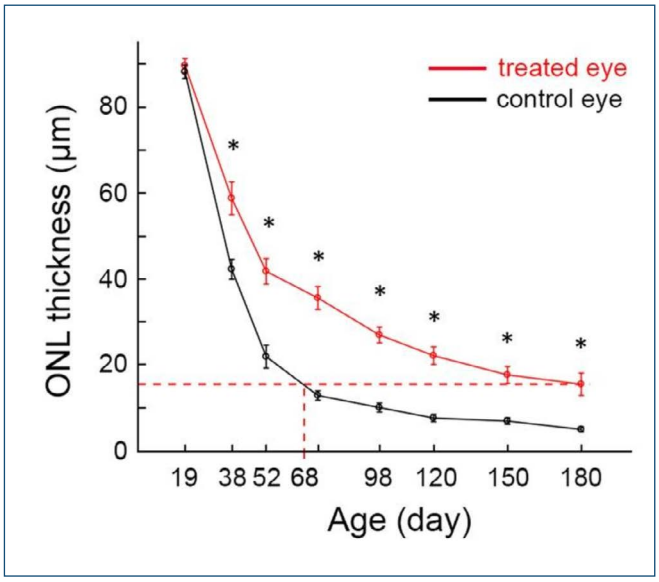


Figure 3. Fluorescein angiography image: laser spots applied to retina. The distanced equivalent to 1 day (top) or 5 day (bottom). Ocular CT: photoreceptor damage (arrows) after photobiomodulation therapy.[8]

from the first 20/50 to 20/20. The visual field regained its normal perimeter, but retained the remaining absolute mid-peripheral circular scotoma.[13]

Other studies in rats have shown results from eye examinations. Fluorescein angiography (FA) shows a hyperreflex patch at the site where the laser treatment was applied, indicating destruction of the RPE (Figure 3). The damage to the photoreceptors caused by the laser was clearly visible in the ocular CT (OCT) (Figure 3)[8,9]

Kang et al.[8] divided the sample into six subgroups with different diameter of spot spacing, and the b-wave (Figure 4) proved that the optimal laser pattern density for functional preservation was 1.5 d. They also compared with fellow eye as control. Conservation of outer nuclear layer (ONL) was clearly observed in OCT and multifocal electroretinogram (mfERG) (Figure 6) until the end of the follow-up period (P180) in the laser-treated eyes, but ONL was indistinguishable after P98 in the control eye. Histology (Figure 5) also showed that the treated eye had the best-conserved photoreceptor layer with up to 5 rows of photoreceptor nuclei and outer segments, whereas the control eye had discernible light. It was shown that it did not have a receptor layer or its nucleus. As confirmed by other studies, they showed that ONL was about twice as



ONL: outer nuclear layer.

Figure 4. B wave showed outer nuclear layer thickness: significantly higher outer nuclear layer thickness in treated eye, compared to control eye ($p < 0.05$).[9]

thick as laser-treated eyes and had a significantly higher number of photoreceptor nuclei ($p < 0.05$).[1,9,13] In contrast, untreated eyes showed thinning of ONL and severely disturbed retinal morphology.[1] Kirk also reported the similar result with TUNEL+ dying photoreceptors technique. PBM attenuates photoreceptor cell death that is demonstrated on less frequent ONL cells in treated eye.[3]

The other results parameter for PBMT was the upregulation of CO reported by Kirk et al. CO is an important mitochondrial enzyme and is highly expressed in non-degenerative retinas where mitochondria are concentrated, especially in the internal segment, as well as in outer plexiform layer (OPL), inner plexiform layer (IPL), and ganglion cell layer (GCL). In control rats, CO was not strongly expressed in the inner segment, while treated rats showed the most significant increase in CO expression in the inner segment.[3]

In RP, oxidative stress can cause mitochondrial dysfunction, leading to the death of photoreceptors in the retina. This formula: NADH redox ratio (RR) = NADH / FAD (oxidized form of FADH2) is used to provide a quantitative indicator of changes in mitochondrial oxidation state associated with this disease.[1,12]

Mitochondrial NADH RR of animal RP models prior to PBM treatment decreased by 24%,[12] and Gopalakrishnan et al showed that 830 nm PBM maintained the redox state of the mitochondria, marked by increased NADH and reduced FAD in rats, resulting in a higher RR (28%).[1] Higher NADH-RR has been shown to reduce oxidative stress and improve or protect

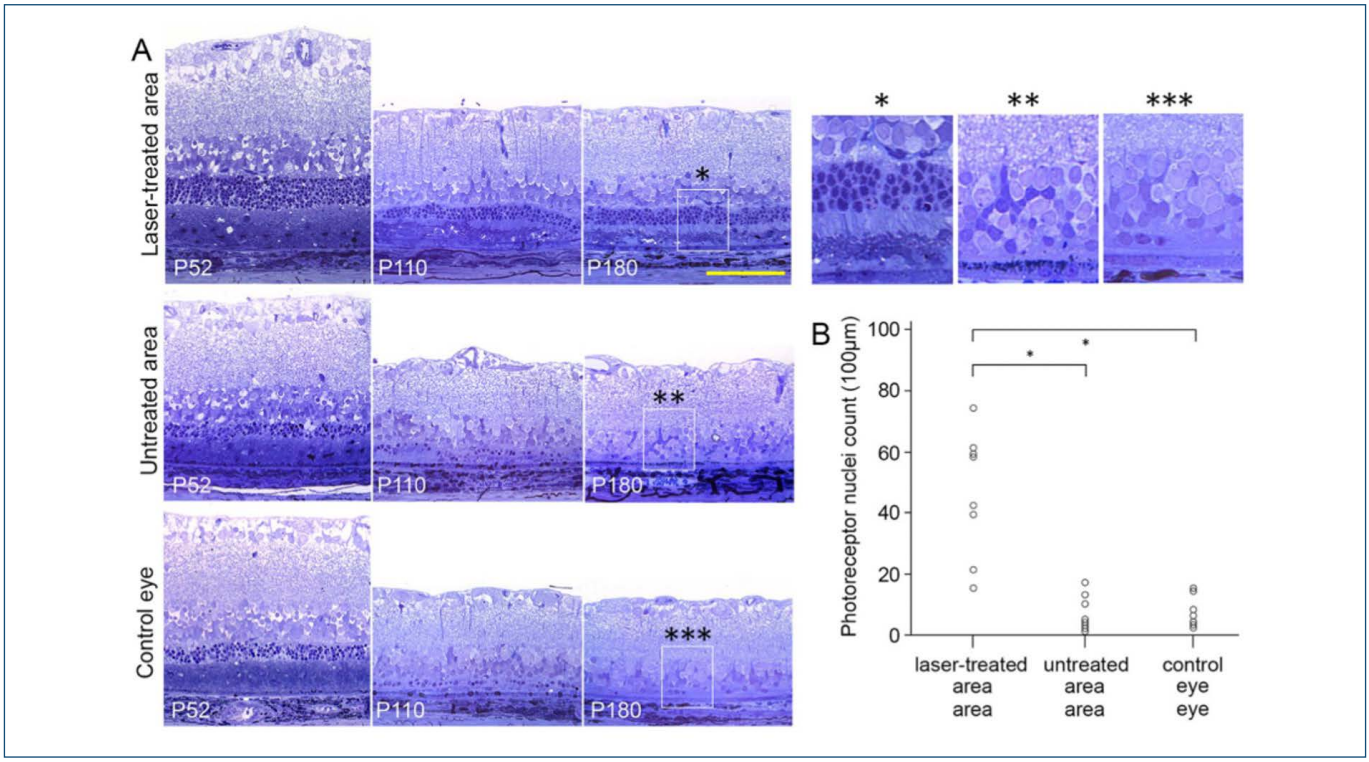
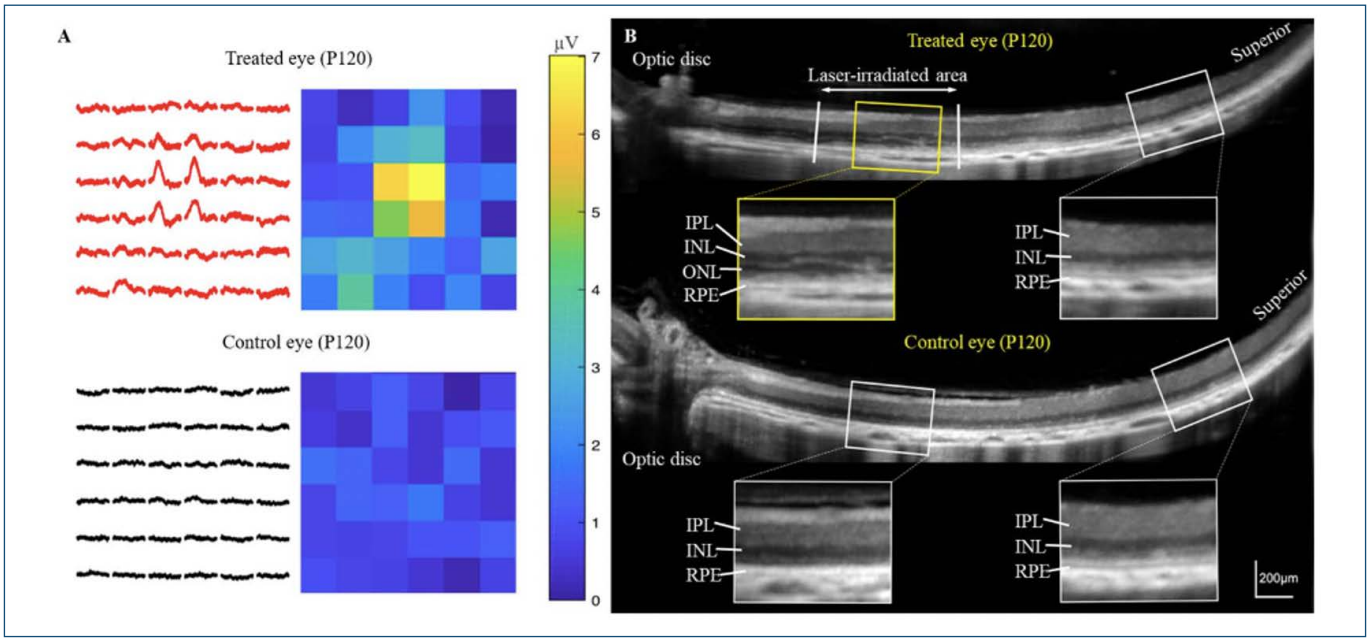


Figure 5. Histology of outer nuclear layer thickness. (A) The representative histology of 52, 110, and 180-day old RCS rat retinas from laser-treated area (upper row), untreated retina in the same eye (middle row), and contralateral control eye (bottom row). Much thicker outer nuclear layer is evident in the treated area than in both controls. (B) Number of the photoreceptor nuclei per 100 μm in the laser-treated retina, untreated retina, and control eyes ($p < 0.001$).[9]



IPL: inner plexiform layer; INL: inner nuclear layer; ONL: outer nuclear layer; RPE: retinal pigment epithelium

Figure 6. Multifocal electroretinogram and ocular CT showed outer nuclear layer thickness. (A) Multifocal electroretinogram responses were detected only in the laser-treated area, while the others were nearly flat. (B) The outer nuclear layer is still present (upper yellow box) in the laser-treated zone, unlike the untreated retina (upper white box) in the same eye, and the fellow eye (two lower white boxes).[8]

Tabel 2. Risk of bias within individual studies included in this review

Reference	Potential for confounding	Eligibility criteria	Intervention	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection in reported result
Gopalakrishnan et al.[1]	Probably no	Unclear	Yes	No	No	Yes	Yes
Kirk et al.[3]	No	Yes	Yes	No	No	Yes	Yes
Kang et al.[8]	Probably no	Yes	Unclear	No	No	Yes	Yes
Lorach et al.[9]	Probably no	Yes	Unclear	Probably no	No	Yes	Yes
Ivandic et al.[13]	No	Yes	Yes	Probably no	No	Unclear	Yes
Ghanian et al.[12]	No	Yes	Yes	No	No	Yes	Yes
Gkotsi et al.[14]	No	Yes	Yes	No	No	Yes	Yes

Studies are assessed on relevant items from Cochrane Checklist. Potential for confounding: confounding effect of intervention. Eligibility Criteria: selection of participants based on characteristics observed before the intervention. Intervention: intervention groups clearly defined. Deviation from intended intervention: deviations that happen in usual practice following the intevention. Missing data: participants excluded due to missing data. Measurement of outcomes: methods of outcome assessment comparable across intervention groups. Selection in reported result: reported effect likely to be selected based on the result from analysis of the intervention-outcome relationship.

mitochondrial function. This has also been confirmed by Zahra et al. showing a 20% increase in NADH-RR.[12]

Gkotsi also reported another marker of oxidative stress and mitochondrial function including COX (an important component of the ATP respiratory chain) and acrolein (a marker of oxidative stress). This study reports a significant increase in retinal ATP of less than 20% manifested by an increase in COX expression and a decrease in acrolein observed in the outer retina by immunohistochemical staining after PBM therapy.[14]

Based on all the studies in our literature, there was no evidence of damage to the normal retina after PBM therapy.

Risk of bias within studies

Risk of bias evaluation of individual studies revealed that most studies clearly defined the eligibility criteria of participants, intervention status, controlled confounding. There is no missing data and deviation from intended intervention. Explanation of exclusions, and any quality assurance for certainty of the employed methods were less consistently declared. Selection in reported result likely to be selected based on the result from analysis of the intervention-outcome relationship. After assessing studies, we found that our study was at low risk of bias. Our risk of bias evaluation of individual studies are summarized in Table 2.

Studies are assessed on relevant items from Cochrane Checklist. Potential for confounding: confounding effect of intervention. Eligibility Criteria: selection of participants based on characteristics observed before the intervention. Intervention: intervention groups clearly defined. Deviation from intended intervention: deviations

that happen in usual practice following the intevention. Missing data: participants excluded due to missing data. Measurement of outcomes: methods of outcome assessment comparable across intervention groups. Selection in reported result: reported effect likely to be selected based on the result from analysis of the intervention-outcome relationship.

DISCUSSION

Although the result of eye examination shows changes in positive way, such as delay loss or prolonged photoreceptor survival and preserved higher retinal function, the actual mechanism leading to photoreceptors survival after PBMT remains unknown.[8,9] Several mechanisms have been proposed, including enhancement of RPE phagocytosis after PBMT, suppression of photoreceptor apoptosis by expression of neurotrophic factors such as basic fibroblast growth factor and ciliary neurotrophic factor, activation of other phagocytic cells such as microglia and macrophages after PBMT. Another mechanism could be the balance between supply and demand in the recycling of outer segments. That is, if the load on the lost outer segment is low enough, even diseased RPE cells can maintain them and prevent the accumulation of the outer segment. As a result, PBMT elimination of some fraction of photoreceptors can reduce daily load of shed outer segment to sustainable levels.[8,9] Reducing the number of photoreceptors reduces the metabolic load on the affected vascular system and reduces the production of angiogenic factors from the hypoxic retina, thereby protecting the central retina from neovascularization.[9]

As reported by Ivandic et al., the results of the regeneration process leading to the recovery of cellular function are seen in improved vision and visual field. This process may involve the rescue of a large population of receptor cells that have become dysfunctional due to the entry into the -still reversible- pathway to apoptotic cell death. In addition, PBMT may have promoted axon, synapse, dendrite regeneration, and qualitative and quantitative improvement of cell-cell connections.[13]

Mitochondrial restore and attenuation of oxidative stress are vital to the long-time period survival of the retina. Accordingly, understanding the mechanisms concerned in photoreceptor and retinal degeneration are essential to developing therapeutic strategy to deal with those diseases.[1,12]

Previous studies have reported significant redox changes in mitochondrial redox potentials in the early stages of rat RP. Mitochondrial metabolic coenzymes (NADH and FADH2) are the major electron donors and receptors involved in oxidative phosphorylation. Increased ROS production and mitochondrial dysfunction are characterized by the accumulation of oxidized forms (NAD and FAD) of mitochondrial coenzymes as a result of progressive retinal degeneration in RP rats. Chronic proteotoxic stress distorts the energy profile of photoreceptors, causing metabolic imbalances, mitochondrial disorders, retinal degeneration, and this in the retina using PBMT to normalize metabolic function can reduce toxicity.[1,12]

FR/NIR light has been shown to alter the redox state of cytochrome c oxidase and increase the electrochemical proton gradient, thereby increasing mitochondrial membrane potential and ATP synthesis. There is also evidence that FR / NIR light dissociates nitric oxide (NO) from the CcO binding site and increases CcO activity. The NO released from the CcO diffuses into the cytosol. Redox and NO changes have been shown to activate transcription factors.[1]

It is important to acknowledge the limitations of our study. Several studies only have a few participants, so they do not provide a long-term outcome in RP. There are also limitations in the review process due to the small number of studies on PBMT on RP. Further research in humans on a large scale is needed to determine the delivery dose parameters.

CONCLUSION

Photobiomodulation therapy, which is a photobiomodulation laser with a wavelength of far-red/near-infrared (600 to 1,000 nm) can penetrate the retina and optic nerve. This is evidenced by functional and outer nuclear layer preservation, decline waveform, disruption of retinal pigment epithelium, and preserved photoreceptor nuclei twice thicker. Photobiomodulation therapy also increases retinal mitochondrial cytochrome oxidase and preserves mitochondrial redox state, which reveals significant recovery of photoreceptors cell function. These change leads to clinical improvement in visual acuity and visual fields, therefore photobiomodulation therapy can be a promising therapeutic strategy for retinitis pigmentosa in the long term period.

SUPPLEMENTARY APPENDIX

More regressions were run and could not be included in the article. The interested reader can find them in a supplementary appendix online.

AUTHOR'S CONTRIBUTIONS

All authors declare having participated actively in this study and article writing and partly responsible for the content of writing, including the preparation and writing of concepts, designs, analysis, or revision of the article.

Conception and design: IBA, YSA
Collection and assembly of data: IBA, YSA
Data analysis and interpretation: IBA, YSA
Manuscript writing: all authors
Final approval of manuscript: all authors

ETHICAL STATEMENT

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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