applied sciences

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Review

Current Applications and Future Perspectives of Photobiomodulation in Ocular Diseases: A Narrative Review

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Abstract: The present article provides an overview of photobiomodulation (PBM), also known as low-level laser light therapy (LLLT), which has garnered attention in ophthalmology for its potential therapeutic benefits in various ocular diseases. Photobiomodulation involves the use of low-intensity lasers or light-emitting diodes to stimulate biological processes in target tissues without causing thermal damage. This article discusses how PBM has been explored across various ocular conditions, including ocular surface diseases, age-related macular degeneration, diabetic retinopathy, myopia, amblyopia, and glaucoma. It summarizes findings from human studies and clinical trials demonstrating positive outcomes of PBM treatment in these areas. Moreover, the article emphasizes the importance of establishing standardized treatment protocols in terms of session duration and frequency, light type, and patients' inclusion criteria to further validate the role of PBM in managing ocular diseases.

Keywords: PBM; LLLT; eye; dry eye; AMD; diabetic retinopathy; myopia

Citation: Cannas, C.; Pintus, B.; Corgiolu, L.; Borrelli, E.; Boscia, G.; Toro, M.D.; Giannaccare, G. Current Applications and Future Perspectives of Photobiomodulation in Ocular Diseases: A Narrative Review. *Appl. Sci.* **2024**, *14*, 2623. https://doi.org/10.3390/app14062623

Academic Editor: Alexander N. Pisarchik

Received: 17 February 2024
Revised: 15 March 2024
Accepted: 19 March 2024
Published: 21 March 2024

1. Introduction

Photobiomodulation (PBM) represents a technology that has been widely used in various medical fields, such as dermatology, psychiatry, oncology, stomatology, physiatry, and, recently, in ophthalmology. Also known as low-level laser light therapy (LLLT), it is based on the use of lasers or light-emitting diodes (LEDs) that produce low intensity light. It is non-invasive and has been shown to decrease inflammation and provide pain relief [1]. The history of PBM accidentally started in 1967 when Mester and collaborators studied the effect of a low-level red laser treatment on shaved murine skin in which a tumor had been previously surgically implanted. They found no evidence in neoplastic changes but acceleration in hair regrowth. Furthermore, they noted an improved wound healing in various models following irradiation with defocused red laser light [2,3]. Moreover, the National Aeronautics and Space Administration (NASA) explored the use of PBM to enhance healing processes in space [4]. The key distinction of PBM therapy from other medical laser or LED devices lies in the intensity of the light used [5]. In fact, PBM employs moderate and non-destructive light intensities, characterized by specific wavelengths, fluences, and power densities [6]. The radiation used in PBM therapy falls within the visible and near-infrared spectral range and is absorbed by endogenous chromophores in target tissues. This absorption triggers photophysical and photochemical events at various biological scales without causing thermal damage [7].

Understanding the underlying mechanisms of low-level light therapy (LLLT) remains a topic of debate within the scientific community. According to the main theory proposed

by Karu et al., cytochrome C oxidase (Cox) acts as a light acceptor following initial photon interaction, leading to an increase in mitochondrial membrane potential. However, it is believed that tissue effects may vary and follow different pathways.

A comprehensive analysis of potential mechanisms of action at the molecular, cellular, and tissue levels is provided in the article by Freitas et al. At the molecular level, various potential mechanisms of action have been identified, including activation of chromophores such as Cox, retrograde mitochondrial signaling, light-sensitive ion channels, and direct effects mediated by free light on the cell. Additionally, various signal transduction pathways are involved, such as ATP, cAMP, ROS, Ca^{2+}, and NO, along with the activation of various transcription factors and effector molecules such as transforming growth factor-beta (TGF-β), oxidative stress, pro- and anti-inflammatory cytokines, brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), and keratinocyte growth factor (KGF), along with heat shock proteins (HSP).

At the cellular level, LLLT appears to have an anti-inflammatory and cytoprotective effect, promoting proliferation, enhancing collagen fiber migration in wounds, inducing protein synthesis, and being involved in stem cell proliferation [8–13].

This review aims at providing a concise analysis of its applications in treating various ocular pathologies, including dry eye and ocular surface disease, age-related macular degeneration (AMD), diabetic retinopathy, myopia, amblyopia, retinopathy of prematurity, and glaucoma while considering also other potential future applications.

2. Materials and Methods

A comprehensive search was conducted in the PubMed database using the keywords listed in Table 1. An exhaustive review was carried out, encompassing all studies published in the English language up to January 2024. A total of 457 full-text articles were identified on PubMed, of which 1 was excluded as a duplicate. The remaining 456 articles were evaluated for eligibility. Following a full-text evaluation, 32 articles were included. Additionally, the search was extended to consider 28 relevant references from the chosen articles.

Table 1. Search strategy and key words used during the literature review.

Treatment		Disease
"Photobiomodulation" OR "Low-level light therapy"	AND	"Dry eye disease" OR "Chalazion" OR "Cataract" OR "Meibomian gland dysfunction" OR "Age related macular degeneration" OR "Diabetic retinopathy" OR "Myopia" OR "Amblyopia" "Glaucoma" OR "Retinopathy of prematurity" OR "Ophthalmology" OR "Eye"

3. Current Applications

3.1. Ocular Surface System

3.1.1. Dry Eye Disease—Treatment and Prophylaxis

The understanding of dry eye disease (DED) as a multifactorial condition involving tear film dynamics, ocular surface inflammation, and neurosensory abnormalities has evolved in recent decades, as highlighted by TFOS DWES II definition. A crucial distinction is made between aqueous-deficient and evaporative types, with the latter, often associated with meibomian gland dysfunction (MGD), being more prevalent [14]. Meibomian glands, located in the eyelids, play a crucial role in tear film stability by secreting meibum. In cases of obstructive MGD, the glands undergo pathological changes leading to meibum stasis, duct obstruction, and ultimately acinar atrophy. This process contributes to tear film instability, increased evaporation, and the initiation of a detrimental cycle marked by inflammation and elevated tear osmolarity [15–18].

Photobiomodulation therapy has emerged as a potential treatment for MGD. The hypothesis suggests that PBM stimulates ATP production in the meibomian glands, inducing

endogenous heating and facilitating meibum flow. While there is a considerable body of research on the combined use of LLLT and intense pulsed light (IPL) technologies, the effectiveness of LLLT as the only therapy in DED associated with MGD is an area with limited exploration. Three articles addressing the efficacy of LLLT alone have been identified. Park and collaborators conducted a randomized, double-blind clinical trial involving 40 DED patients, showing positive effects of LED-LLLT. Light irradiation was performed with a LED-based array matrix module with 5 planar panels. For the first 1 min of irradiation, a wavelength of 590 nm in continuous wave and an irradiance of ≈50 $\mu W/cm^2$ were scanned panel by panel for 1 s per panel, giving a fluence of ≈50 $\mu J/cm^2$. At the end of that minute, 830 nm was delivered from all 5 panels at an irradiance of 100 mW/cm^2 for 10 min in continuous wave mode. The system is LED-based, and the irradiance was below the ANSI values for maximum permissible exposure (MPE). The energy density over the entire near field area (encompassing the entire face and orbital area) was therefore ≈60 J/cm^2 per session (HEALITE II, Lutronic, Goyang, Republic of Korea), with a distance between the treatment head and target tissue of approximately 17 cm [19]. Giannaccare and co-authors compared LLLT and IPL both performed using the Eye Light device (Espansione Group, Bologna, Italy), reporting significantly higher improvements in symptoms and tear film volume after LLLT compared to IPL [20]. Additionally, an at-home LLLT miniaturized device called my-mask (Espansione Group, Bologna, Italy) has been introduced in the market, showing positive results without adverse events during a study conducted by the same group of authors. Light irradiation was performed with 15 min of irradiation at 625 nm ± 40 nm wavelength in continuous wave, an irradiance of ≈35 mW/cm^2 and the standard dose transferred to the patient of 32 J/cm^2 [21].

Among the various types of DED, TFOS DEWS II identified the iatrogenic cause owing to different ocular surgeries and, in particular, senile cataract surgery. In fact, patients undergoing this surgery may have pre-existing ocular surface alterations that could either be revealed or exacerbate postoperatively. Diabetic patients are known to be a population more prone to experience this complication. The pathogenetic mechanism is multifactorial, such as surgical technique, duration of the procedure, intensity of microscope light, type of lid speculum, and postoperative topical therapy, among others [22,23].

In a recent randomized controlled double-masked clinical trial, Giannaccare and colleagues studied the effectiveness of LLLT in preventing iatrogenic DED in healthy patients undergoing senile cataract surgery. The study included 153 healthy patients, and 131 of them completed the study. The treatment study was performed using the Eyelight®device (Espansione Group S.p.A., Bologna, Italy) one week before and after surgery. The control group received a simulated LLLT session with reduced (<30%) output. Results showed a statistically significant improvement in ocular surface disease index (OSDI) score after LLLT treatment compared to the placebo group at all time points (1 week and 1 month after surgery). Additionally, there was a statistically significant improvement in NIBUT value 1 month postoperatively [24]. Despite the limitations related to the use of OSDI score for cataract patients with impaired vision and the relatively short follow-up period, this study is the first to highlight the potential role of LLLT for the prophylaxis of iatrogenic DED, opening up a new fascinating scenario that requires future research.

3.1.2. Chalazion

Chalazia are benign granulomatous inflammatory lesions affecting the eyelids, primarily attributed to inflammation of the meibomian gland leading to meibum thickening [25]. These lesions are typically self-limiting with a spontaneous resolution rate of 25% after 6 months; however, in the remaining cases they can become recurrent or chronic [26,27]. In a recent prospective study by Huang and co-workers, the authors found an association between recurrent and multiple chalazia and Demodex infestation, particularly in paediatric patients [28]. Conventional treatments include warm compresses, topical (antibiotic and/or corticosteroid) or systemic medications (e.g., tetracyclines, macrolides), intralesional corticosteroid injections, or surgical procedures like incision and curettage. The efficacy of LLLT

has been explored in a retrospective study conducted by Stonecipher and co-authors. In this study, 26 eyes of 22 patients with chalazia unresponsive to previous pharmaceutical or surgical interventions received a 15 min LLLT treatment. A second LLLT session was applied if there was no evidence of resolution after the first one. Overall, 92% of eyes showed therapeutic benefits with LLLT, while surgery was required only in the remaining few cases. Therefore, LLLT appears to be beneficial in this setting reducing the likelihood of surgical intervention. In this case, the LLLT device investigated was part of the Eye-light® or Epi-C PLUS system, depending on if the treatment was performed, respectively, outside USA or in the USA. The wavelength was 633 ± 10 nanometers with an emission power of 100 mW/cm^2. The total fluence in the treated area was 110 J/cm^2 [29].

3.2. Retina

3.2.1. Age-Related Macular Degeneration

Age-related macular degeneration (AMD) is a leading cause of vision impairment, especially in developed countries, where it stands as a major contributor to irreversible blindness among the elderly [30]. AMD involves pathological alterations affecting the deeper retinal layers of the macula and the surrounding vasculature, culminating in the loss of central vision. The hallmark clinical observation in AMD is the accumulation of retinal deposits known as drusen, which may be the first sign of the "dry" form of the disease. This dry form, being the predominant morphological type, can progress to the "wet" or neovascular AMD. In neovascular AMD, central choroidal neovascular membranes (CNV) can form, leading to hemorrhaging and exudation within the retina, ultimately resulting in profound vision impairment [31].

The AREDS classification system, widely used for age-related macular degeneration (AMD), categorizes AMD into different groups. The control group (AREDS 1) shows no or few small drusen. Early AMD (AREDS 2) involves numerous small drusen, some larger drusen, or RPE abnormalities. Moderate AMD (AREDS 3) includes medium-sized drusen and at least one large druse, with geographic atrophy not in the central macula. Advanced AMD (AREDS 4) comprises geographic atrophy of the RPE involving the macula and neovascular maculopathy, including CNV, retinal detachment, exudation, and fibrovascular proliferations, often leading to a discoid scar [32,33]. Photobiomodulation is emerging as a potential treatment for dry AMD. This technique employs three distinct laser wavelengths (590 nm, 660 nm, and 850 nm) to primarily focus on the mitochondrial electron transport chain [34,35]. The initial report of the use of PBM to treat AMD in humans dated 2008, when a prospective study involved 348 eyes and 203 patients affected by dry and wet AMD, using a semiconductor laser diode with continuous emission (780 nm, 7.5 mW, 292 Hz). The findings demonstrated enhanced visual acuity for both types of the disease, along with a reduction in metamorphopsia, scotoma, and dyschromatopsia. Patients with wet AMD experienced improvements in edema and bleeding. The improved vision persisted for 3 to 36 months after the treatment. Notably, no changes in visual acuity were reported in the control group [36]. The ALIGHT was a single-center randomized controlled trial (RCT) conducted at Bristol Eye Hospital in Bristol, UK. The study included 60 participants with AREDS grades 2 to 4 and an ETDRS BCVA score of 0.3 logMAR or better in the study eye. Participants were randomly assigned to receive LED-PBM (505 nm) treatment or no treatment in the study eye. Photobiomodulation (PBM) was administered for 8 h every night for 12 months using the Noctura 500 mask (PolyPhotonix Medical, Ltd., Sedgefield, UK). All participants were concurrently undergoing ranibizumab injections for neovascular AMD in the fellow eye. Investigators conducted monthly assessments using optical coherence tomography (OCT) imaging to measure drusen volume and detect the development of neovascular AMD. ALIGHT demonstrated that there was no significant difference in Best-Corrected Visual Acuity (BCVA) between participants who received single-wavelength PBM and those who did not after one year. Furthermore, light therapy did not yield a significant impact on the progression of early age-related macular degeneration (AMD) throughout the 12-month duration [37].

Additionally, in the review published on the Cochrane Library conducted by Henein and Steel, it is emphasized that in the ALIGHT study, researchers did not adhere to CONSORT guidelines (Ioannidis 2004) when reporting adverse events, as they did not provide overall absolute risk per arm or per adverse event type data. The seriousness of adverse events was not fully disclosed, and there was uncertainty regarding whether any adverse events were recurrent in the same participant [38]. In the TORPA 1 trial, 18 eyes classified as AREDS stages 2 to 4 of patients aged 50 or older with a visual acuity between 0.1 and 1.0 were included. Devices used were Warp10 (Quantum Devices) (670 nm ± 15 nm at 50–80 mW/cm^2, 4–7.68 J/cm^2, for 88 ± 8 s) and Gentlewaves (Light Bioscience) (590 nm ± 8 nm at 4 mW, 790 nm ± 60 nm at 0.6 mW, for 30 s). Individuals received a direct transpupillary treatment 18 times within a span of 6 weeks using both devices. They reported an improvement in both visual acuity and contrast sensitivity at 12 months [39]. In the TORPA 2 trial, 42 eyes were treated with the same devices of TORPA 1 trial according to protocol consisting of 3 treatments per week for 3 weeks. A significant improvement in visual acuity, contrast sensitivity, and anatomical parameters such as drusen volume was reported [40]. These results are consistent with those reported in LIGHTSITE I, II, and III trials. LIGHTSITE I is a randomized, sham-controlled, single-center study investigating the impact of PBM on AMD. The Valeda Light Delivery System (LumiThera, Inc., Poulsbo, WA, USA) (590 nm, 5 mW/cm^2, 70 s, 670 nm, 65 mW/cm^2, 70 s, 850 nm, 8 mW/cm^2, 180 s) was used in patients with dry AMD who received 9 treatments (3 treatments per week for 3 weeks) at baseline and after 6 months. The efficacy of PBM appeared to require periodic retreatments, typically ranging from 4 to 6 months, indicating that although significant improvements in visual acuity and contrast sensitivity are initially achieved, these effects are not sustained over the long term without follow-up treatments [41]. The LIGHSITE II study was a double-masked, randomized, sham-controlled, parallel group, multicenter prospective study that investigates the safety and efficacy of PBM treatment in 44 eyes of patients with intermediate non-exudative AMD. Thirty-five percent of the eyes which completed all PBM sessions with the Valeda System showed an improvement in visual acuity. Furthermore, the study found that an increase over time of macular drusen volume was registered in the sham group but not in the PBM-treated group. Although both PBM and sham groups exhibited a growth in geographic atrophy lesions during the study period, the PBM group demonstrated a reduced growth rate over the course of 10 months. However, the study comes with several limitations. Firstly, the variation in disease severity between the treatment and control groups at the beginning makes it more challenging to interpret the results accurately. Additionally, a notable limitation is the small number of participants who actually completed the planned treatment in the LIGHTSITE II study, with only 27 subjects receiving it [42,43]. LIGHTSITE III is a prospective, randomized controlled trial compelling evidence of enhanced clinical and anatomical outcomes in individuals with intermediate dry AMD following PBM performed with the Valeda System. A total of 148 eyes of 200 patients were included, most of them belonging to AREDS 3 stage. Notably, in the preliminary results reported at 13 months, the PBM group demonstrated a significant improvement in visual acuity and a reduction in the occurrence of new-onset geographic atrophy. However, regarding BCVA, it is worth asking whether a mere 2-letter improvement holds clinical significance. However, the transition rate from non-exudative to exudative AMD was higher in the group receiving PBM compared to the control group [44]. In a pilot study by Grewal and colleagues, the authors aimed at evaluating the effect of 670 nm light on dark adaptometry, considered as a biomarker for AMD. Surprisingly, the light exposure did not impact the AMD group but reduced rod-recovery time in healthy aging eyes. Structural volumetric analysis revealed no significant alterations in drusen volume or beneficial effects on the outer nuclear layer after 12 months. Notably, the study did not investigate drusen regression, and the structural analysis did not support positive outcomes reported in earlier studies. Limitations encompassed the absence of a control arm, potential selection bias, and a relatively small sample size [45]. Benlahbib and collaborators published the results of a pilot study

in which the Valeda System with 3 different wavelengths (590 nm; 4 mW/cm^2, 660 nm; 65 mW/cm^2, 850 nm; 0.6 mW/cm^2) was employed. The study aimed at assessing the effects of PBM on visual acuity and morphological changes in patients with large soft drusen and/or drusenoid pigment epithelial detachment associated with dry AMD. Twenty eyes underwent PBM treatment with 2 sessions per week for 5 weeks. The results showed a significant improvement in visual acuity, drusen volume, and thickness at the 6-month follow-up visit [46]. Despite all the positive effects described in the above-mentioned studies, treatment-related adverse effects were reported. Benlahbib and co-authors described a slight increase in geographic atrophy area and a drusenoid pigment epithelial detachment rupture in a patient [46]. In addition, in late 2023, Parodi and colleagues documented a case involving a 63-year-old woman with a subfoveal drusenoid pigment epithelium detachment (D-PED) that collapsed two weeks after the last session of (PBM). The patient received three PBM sessions per week for three weeks using the Valeda Light Delivery System by LumiThera Inc. This is the first report of acute macular atrophy development. While the imaging characteristics of this case may not strongly suggest a PBM-related complication, the brief duration between the last visit and atrophy emergence implies that PBM might expedite the natural progression of D-PED, leading to atrophic changes. This case report suggests that caution is recommended when employing PBM in the treatment of eyes with D-PED exhibiting outer retinal layer thinning or posterior hypertransmission, as this therapeutic approach may accelerate macular atrophy [47]. Currently, the ELECTROLIGHT study (NCT04522999) is ongoing and aims at evaluating the impact of PBM therapy by recording electroretinograms in patients with dry AMD using the Valeda System. A total of 23 eyes from 15 patients with intermediate dry AMD receiving PBM treatment have been enrolled and various visual function parameters were assessed. Another prospective multicenter randomized controlled trial named DRUSEN (NCT06046118) employing the Eye Light device is currently recruiting patients. Treatment consists of two phases: (i) 300 s of continuous yellow light with eyes closed + 60 s of pulsed yellow light with eyes opened; (ii) 300 s of continuous red light with eyes closed + 60 s of pulsed red light with eyes opened. Patients undergo two cycles of treatment: the first one consisting of 8 sessions (2 per week for 4 weeks) and the second one consisting of 6 sessions (2 per week for 3 weeks).

3.2.2. Diabetic Retinopathy

Diabetic retinopathy (DR) is a common microvascular complication that occurs in individuals with diabetes mellitus [48]. Worldwide, over 100 million individuals are dealing with DR, and it stands out as a primary cause of vision loss and blindness, particularly in the working-age adult group [49,50]. Multiple studies explored the potential of PBM in the setting of DR. In 2022, Tang and co-authors [51] guided a pivotal transition from animal studies to human application in cases of diabetic macular edema that did not involve the fovea. Despite promising results in reducing macular thickness, the small sample size raised caution in drawing definitive conclusions. The potential benefits underscore the need for larger investigations to establish optimal treatment parameters and address safety concerns, particularly in patients with pre-existing risk factors. Shen and colleagues explored different energy levels of 670 nm light, adding valuable insights, and emphasizing the importance of dose optimization. The observed maximal reduction in central macular thickness at a specific energy level of 100 mW/cm^2 suggests the need for precise dosing in PBM treatment [52]. Another research by Chen and co-workers supported the safety and efficacy of PBM in treating diabetic macular edema. The authors observed improvements in visual acuity, retinal findings and thickness suggesting positive outcomes and encouraging additional exploration of PBM's potential in this field [53]. Kaymak and co-authors reported the same improvements in visual acuity and retinal findings of patients with diabetic macular edema using the Valeda multiwavelength PBM approach [54]. On the contrary, it is crucial to highlight the clear contrast between these results and those obtained in the study conducted by DCRC, in the AE protocol. The phase 2 randomized controlled trial currently stands as the largest randomized controlled trial investigating the efficacy of PBM on

DME. A total of 135 adults were enrolled, 69 were assigned to receive PBM treatment, and 66 received placebo. The results, while confirming the safety of PBM, distinctly underscore the lack of scientific evidence regarding its efficacy in terms of anatomical and functional improvement. During the 4-month study period, no statistically significant improvements were observed in the central subfield thickness of optical coherence tomography (OCT CST). The OCT CST increased by approximately 13 µm in the PBM group and 15 µm in the placebo group. Additionally, central-involved diabetic macular edema (CI-DME) was found in 90% of eyes treated with PBM and 86% of eyes treated with placebo at the 4-month mark, with no significant differences between the two groups. Furthermore, there was a slight decrease in visual acuity (VA) in both groups, with an average of −0.2 letters in the PBM group and −0.6 letters in the placebo group [55].

3.2.3. Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is a vascular disorder that impacts infants born extremely premature or with low birth weight. The worst scenario of ROP is the occurrence of retinal detachment with subsequent blindness. The risk of these complications has been mitigated through vigilant screening and prompt interventions such as laser photocoagulation and anti-VEGF intravitreal injection. Despite these efforts, ROP continues to be the primary cause of visual impairment in children [56]. In 2020, Kent and co-authors conducted a randomized controlled study examining the effectiveness of PBM using 670 nm red light in premature neonates with ROP. A 670 nm LED was placed on the isolette 20–25 cm above the baby 15 min each day and provided 9 J/cm^2 using a Warp 75 LED device (Quantum devices, Inc., Barneveld, WI, USA) until 34 weeks corrected gestational age. The pilot study aimed at assessing treatment feasibility and determining whether the interval and the dose, based on animal studies, yielded similar results in reducing ROP. The study suggested that 670 nm red light treatment did not significantly impact the growth parameters of preterm neonates but showed a trend towards a lower incidence of ROP, though not reaching statistical significance [57].

3.3. Myopia

Myopia is a type of refractive error whose spherical equivalent is equal or higher than 0.50 diopters (D). It is classified as high when the spherical equivalent is equal or higher than 5.0 D or when the axial length is higher than 26 mm [58]. Myopia is associated with various ocular complications such as myopic macular degeneration, retinal detachment, cataract, and open-angle glaucoma [59]. The prevalence of myopia is expected to increase in the next years, and a meta-analysis estimated that by 2050, half of the world's population will be affected by myopia that will be high in 10% of subjects [60]. The increase in myopia prevalence is believed to be caused, in addition to genetic factors, by modern lifestyle characterized by reduced outdoor time for children and increased activities involving near vision, such as the use of digital devices [61–63]. The mechanism of action of PBM therapy in slowing myopia progression is not entirely clear. Cohen and co-authors highlighted how light affects dopamine metabolism in the retina [64]. However, it seems that depending on the wavelength, blue, red, and UV lights act differently. In particular, red light is that one most associated with slowing myopia [56,65]. The most recent meta-analysis published in December 2023 demonstrated statistically significant results of PBM therapy in controlling axial length and spherical error refraction compared to the control group [66]. These data are consistent with those provided by the previous meta-analyses [67,68]. Data from a secondary analysis of a multicenter randomized controlled trial [69] highlighted the correlation between PBM therapy and increased choroidal thickness at the macular level [70]. In the trial was used a desktop light therapy device (Eyerising [Suzhou Xuanjia Optoelectronics Technology, Suzhou, China]), which consists of semiconductor laser diodes which deliver low-level red light with a wavelength of 650 ± 10 nm at an illuminance level of approximately 1600 lux through the pupil to the fundus. Additionally, it has been observed that changes in choroidal thickness at the macular level in the first 3 months

are predictive of positive response at 1 year [71]. The efficacy of PBM therapy is dose-dependent and closely linked to patient compliance [69]. Despite PBM therapy being proven to be safe and free from complications even in the 2-year study conducted by Xiong and co-authors, it is essential to extend the follow-up to highlight any potential long-term adverse effects. In the same study, a rebound effect was documented at the end of 1 year of PBM therapy [72].

3.4. Amblyopia

Amblyopia is the most prevalent form of vision impairment among children, impacting approximately 2–4% of the population [73,74]. In the literature, there are a few studies examining the effectiveness of LLLT in treating amblyopia. However, these studies are somewhat outdated, and despite showing positive results, no further studies have followed suit. For these reasons, we find it appropriate to report what we uncovered in the literature for the sake of completeness, while underscoring the limitations of the evidence. The study conducted by Ivandic explored the effectiveness of LLLT in treating adolescent and adult patients with amblyopia. In this single-blinded, placebo-controlled study, 178 patients with amblyopia caused by ametropia or strabismus were treated with LLLT for an average number of 3.5 sessions. No occlusion was applied, and no additional medication was administered. The research suggested that LLLT enhanced visual acuity in adults with amblyopia, showing statistically significant improvement in over 90% of treated eyes. An improvement of three or more lines was reached in 56.2% and 53.6% of amblyopic eyes secondary to ametropia or strabismus, respectively. The treatment effect was maintained for at least 6 months [75].

3.5. Glaucoma

Glaucoma represents a neurodegenerative disorder characterized by the progressive degeneration of the optic nerve head and retinal nerve fiber layer functionality [76]. The pivotal determinants of glaucoma encompass age, ischemia, and structural factors. Aging, marked by cellular senescence and functional cell deterioration, precipitates an augmented incidence of glaucoma [77]. Concurrently, structural factors, chiefly influenced by heightened intraocular pressure (IOP), delineated as the ratio of discharged aqueous humor to that produced by the ciliary body, wield substantial influence. Nonetheless, glaucoma can manifest even within the statistically normal IOP range (10–21 mmHg), named as normal-tension glaucoma (NTG). It has been demonstrated that mitochondrial dysfunction is the primary cause of optic neuropathies such as Leber's optic neuropathy, dominant optic atrophy, and some cases of glaucoma. It has also been observed that retinal ganglion cells can initiate rapid degradation of damaged mitochondria in response to acute mitochondrial damage and activate swift mitochondrial regeneration. This process is triggered by the AMPK-PGC1α biogenesis axis, which is, in turn, inhibited by TBK1 [78]. Osborne and co-authors empirically demonstrated the adverse effects of blue light on the mitochondria of retinal ganglion cells. Furthermore, it has been postulated that blue light inflicts damage upon mitochondrial electron transport chain-related enzymes, specifically flavin and cytochrome C oxidase (CCO), instigating the generation of photochemical effects and ROS [79]. While ROS regulation is typically governed by antioxidants, eyes deformed by ischemia or myopia undergo an excessive production of ROS and mitochondrial DNA damage due to prolonged blue light exposure. This intricate cascade culminates in the loss of the visual field through a sequence of events leading to cellular demise [80]. Various studies substantiate that blue light activation induces both apoptosis and apoptotic necrosis in retinal cells, potentially underpinning the onset or exacerbation of glaucoma [81–84]. The beneficial role of red light is centered on the activity of CCO, which reduces one molecule of oxygen to form two water molecules, stimulating ATP production through the proton gradient. In eyes damaged by myopia or ischemia, there is a decrease in oxygen concentration and an increase in nitric oxide concentration, which has a higher affinity for CCO, inhibiting its activity and consequently ATP production. Red light enhances the activity

of CCO by photodissociating nitric oxide from CCO [78]. Some studies demonstrated the efficacy of PBM therapy in the treatment of glaucoma. It is observed that PBM has both a hypotensive and neuroprotective effect [85]. A study conducted on 20 glaucomatous patients divided into two groups demonstrated a significant reduction in IOP in the group treated with "Thera-Red" PBM therapy, while the placebo group did not show a significant reduction in IOP [86]. Although we cannot rely on the clinical evidence from a single case report, it is interesting to note that a patient with geographic atrophy associated with a neurodegenerative disease, treated with non-invasive PBM therapy not directly applied to ocular tissues, showed neurological improvements and positive ocular effects, including a reduction in intraocular pressure (IOP) [87]. In a murine model with induced acute glaucoma attack, PBM therapy demonstrated protective effects on ganglion cells, with significantly higher cell count compared to the untreated model and less reduction in ganglion cell layer thickness [88].

4. Discussion and Conclusions

Photobiomodulation is a non-invasive approach that showed promising outcomes in various ocular conditions from the ocular surface to the back of the eye, thus rising to the attention of the ophthalmology scientific community. The results obtained in ocular surface diseases are supported by an extensive literature, opening the novel scenario of using this technology not only for DED/MGD treatment but also for its prophylaxis after cataract surgery. The role of PBM applied in other ophthalmic fields is more contentious. In AMD, as highlighted by Fantaguzzi et al. in their recent review, there are many discrepancies in the robustness of evidence across studies analyzed. Some studies lacked essential elements such as randomization, placebo controls, and adequate sample sizes. Despite examining similar parameters, variations in findings were observed due to differences in baseline conditions. Particularly, evidence regarding reduced drusen volume (DV) was deemed weak, possibly influenced by the natural cycle of drusen material deposition and resorption. Larger sample sizes and precise measurements are warranted to confirm the efficacy of photobiomodulation in reducing DV. Additionally, while drusen resorption is often perceived positively, its long-term benefits remain uncertain and may even contribute to adverse outcomes like geographic atrophy (GA) and advanced macular degeneration. Further research is crucial to understand the mechanisms underlying drusen resorption and its impact on retinal health over extended periods [89].

The application of PBM in treating diabetic macular edema remains a distant prospect, particularly considering the discouraging results from the DCRC.

Regarding the effectiveness of PBM for treating amblyopia, there is controversy over its scientific merit. Despite yielding promising results, the scientific community has not given them much weight, as they have not led to further similar or follow-up studies. We decided to include them in our review for two reasons: to ensure completeness and to cite the studies that later inspired additional research on treating myopia.

It is important to emphasize that currently the literature does not provide sufficient data to assert with certainty the potential role of PBM in the treatment of various ocular pathologies. We cannot exclude long-term side effects or assert that the reassuring results obtained in various studies will persist over time.

In the near future, standardized protocols in terms of number and interval of sessions, parameters used, and light type, along with strict criteria for patient selection, will allow us to provide more robust evidence of the role of PBM in the fields of ocular diseases.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflicts of interest.

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