Review

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Therapeutic Potential of Photobiomodulation in Diabetic Complications

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Diabetes mellitus (DM) and its associated complications, including diabetic kidney disease, neuropathy, and retinopathy, impose significant challenges on healthcare systems due to their high morbidity, mortality, and associated costs. Existing treatments often yield unsatisfactory clinical outcomes, underscoring the need for innovative approaches to mitigate debilitating effects on patients' health-related quality of life. Photobiomodulation (PBM) is a non-invasive treatment that utilizes specific wavelengths of light in the treatment of various medical complications associated with DM. The specific wavelength used during PBM is critical in determining the therapeutic outcomes for managing diabetic complications. This paper aimed to explore the therapeutic potential of PBM in the management of diabetic complications, focusing on blue, red, and near-infrared (NIR) wavelengths. Relevant literature from Google Scholar, PubMed and ClinicalTrials databases from inception to date was searched using the keywords 'photobiomodulation', 'diabetes', 'diabetic complications', 'wound healing', 'neuropathy', 'retinopathy', and 'chronic wounds'. Red and NIR wavelengths are commonly used for a range of complications, while blue light has primarily been explored for treating diabetic wounds due to its antimicrobial nature. PBM treatment parameters for the same diabetic complication vary across clinical trials and preclinical research, with minimal clinical trials conducted on most diabetic complications. This inconsistency hinders the establishment of standardized PBM parameters, particularly concerning the optimal application setting.

Keywords: diabetes mellitus; diabetic complications; photobiomodulation; wavelengths

Introduction

Diabetes mellitus (DM) encompasses a spectrum of chronic metabolic conditions characterized by elevated blood glucose levels, commonly referred to as hyperglycemia [1]. This condition arises due to various factors, including impaired insulin production, insulin resistance, or both, leading to dysregulation of glucose metabolism. Over 537 million adults worldwide were diagnosed with diabetes in 2021, with South Africa having the highest incidence in Africa (4.2 million) [2]. The treatment options for diabetes vary depending on the diabetes type: diabetes type 1 (DT1), in which pancreatic beta cells that produce insulin are attacked by the immune system, or diabetes type 2 (DT2), which is characterized by insulin resistance or abnormal insulin secretion. These conditions are commonly managed by controlling blood glucose levels through lifestyle modifications, medication, and insulin therapy [3].

DM is well known as one of the principal causes responsible for disability, increased health costs, and death in recent years [4]. When left untreated, diabetes can cause severe and life-threatening complications, resulting in the development of cardiovascular diseases, diabetic eye disease, diabetic neuropathy (nerve damage), diabetic kidney disease, and diabetic wounds that often lead to skin ulceration and lower limb amputations. These complications can significantly reduce the productivity and life expectancy of those affected [5,6]. Moreover, hyperglycemia causes inflammation of the blood vessels and impairs the delivery of oxygen and nutrients, resulting in a poor circulatory system and delayed wound healing. Current therapeutic techniques such as glycemic control, pressure regulation, introduction of growth factors, application of skin substitutes, surgical interventions such as pancreas and kidney transplantation, infection management, and wound debridement and dressings are limited in their ability to achieve absolute healing for different complications, often leading to unsatisfactory clinical outcomes [7,8]. Several adjuvant therapeutic methods have been considered for the routine management of diabetic complications, such as photobiomodulation (PBM) [6,9]. PBM is a therapeutic approach that employs specific light wavelengths to promote healing and regeneration in various medical conditions, including diabetic complications. In this paper, we explored the therapeutic potential of PBM in the management of diabetic complications, focusing significantly on the blue, red, and near-infrared (NIR) wavelengths. We also examined how these wavelengths influence wound healing rates. Additionally, we discussed the variations of treatment protocols and address PBM limitations in treating diabetic complications.

Photobiomodulation

PBM, formerly known as low-level laser therapy (LLLT), is a non-invasive therapeutic approach that harnesses the power of low-level light at specific wavelengths to stimulate tissue regeneration, alleviate pain and inflammation, and protect damaged or weakened tissue without causing any thermal damage [10,11]. The application of PBM was discovered in 1968 by Professor Endre Mester *et al.* [12] when they were experimenting with a ruby laser to treat tumors in rats, and surprisingly they detected an increased rate of hair growth and wound healing [12]. As a non-ionizing therapeutic approach, PBM is usually applied within the red (610–750 nm) and NIR (750–1100 nm) electromagnetic spectrum, also referred to as the therapeutic window, to stimulate and expedite cellular modalities [13]. PBM uses an irradiance or power density (measured in mW/cm^2) between 5 mW/cm^2 to 5 W/cm^2, and a power output in the range of 1 mW to 500 mW [14]. Application of red and NIR light to the affected area has been shown to stimulate tissue repair, while blue light (350–500 nm) has been recognized for its antimicrobial therapeutic effects that enhance tissue perfusion, and regulate metabolism by facilitating the restoration of mitochondria that have been inhibited by nitric oxide (NO). This has been achieved through the release of NO, which aids in the transfer of energy to the wounded area [15–18].

During PBM, non-coherent light-emitting diodes (LEDs), or coherent (photon beams have the same frequency) low-powered lasers, are commonly employed to deliver light that penetrates the skin. These photons (light particles) interact with the cells and trigger various biological responses [19]. LEDs are small and durable devices emitting a narrow range of electromagnetic radiation, from ultraviolet (UV) to visible and infrared (IR) light, and can be arranged on small chips or connected to compact lamps with the ability to generate low-intensity light within the milliwatt range [20]. Treatment with these non-ionizing light sources has reportedly been advantageous in stimulating tissue healing, while reducing pain, in various disease models by preventing cell death, boosting cellular energy production (mitochondrial function), and regulating oxidative stress [21].

The effectiveness of therapeutic light interaction with tissue relies on the capacity of a selective chromophore (light-absorbing molecules) to absorb the light, leading to photochemical and photobiological changes [18]. These photons can also be scattered in different directions. Similarly, light interactions can be non-productive if photons are reflected off the surface, or transmitted through it without being absorbed [20]. There is less scattering of light in tissue when using longer wavelengths, and this is due to the wavelength-dependent property of scattering. Tissue penetration depth is limited by scattered light, allowing the incident light to disperse [13]. In this regard, the combination of different wavelengths of light in PBM has been proposed to optimize the management of diabetic complications, as light penetrating deeply into the tissue provide the most favorable outcomes [19]. The appropriate wavelength selection for PBM often depends on the desired tissue penetration depth. Shorter-wavelength light can penetrate superficial tissue, while longer wavelengths can achieve deeper penetration [15,22].

Melanin in the epidermis, hemoglobin in the blood within the dermis, and other chromophores such as opsins

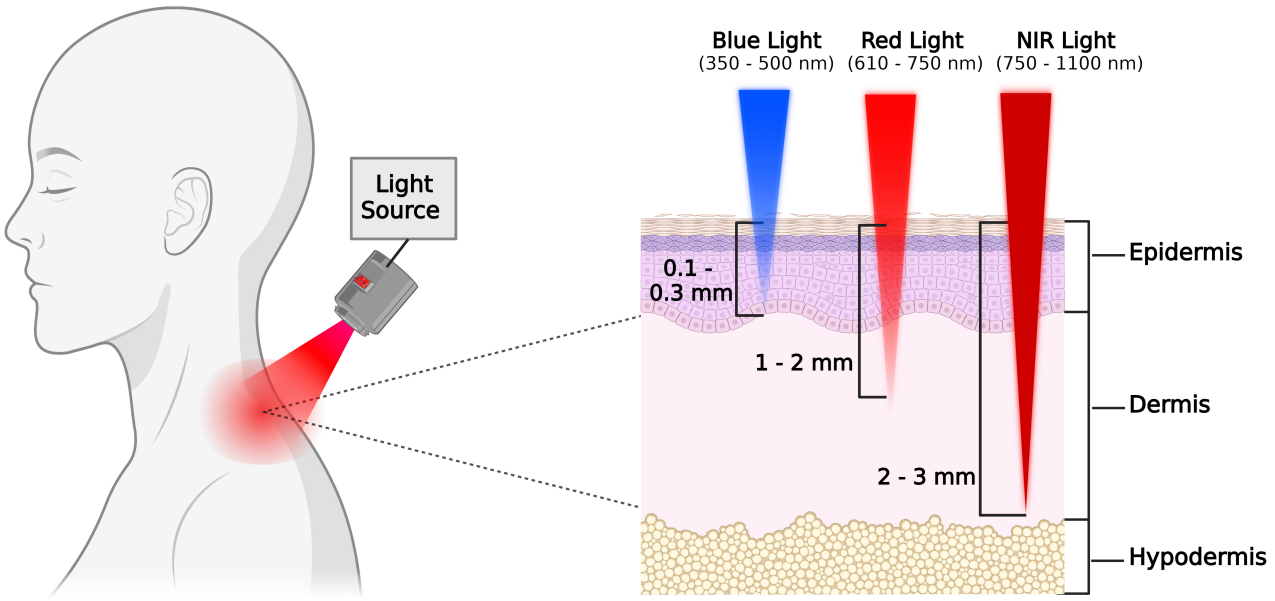

Fig. 1. Tissue penetration depth of light at different wavelengths. NIR, near-infrared. Created with BioRender.com.

and flavins absorb blue light that can penetrate 0.1–0.3 mm into tissue (Fig. 1) [5]. The enzyme cytochrome c oxidase (COX), located in the mitochondrial fourth unit of the respiratory chain (unit IV), and hemoglobin absorb red and NIR light. Red light can penetrate approximately 1–2 mm into the tissue, whereas NIR light penetrates up to a depth of 2–3 mm, affecting cellular processes at the mitochondrial level and resulting in increased blood flow, gaseous exchange, and cellular metabolism [13]. Following the uptake of photons by COX within the red and NIR spectral range, an increase in electron transport occurs, resulting in an elevation of mitochondrial membrane potential (MMP). This in turn leads to an increase in intracellular reactive oxygen species (ROS), adenosine triphosphate (ATP), and NO (Fig. 2). Consequently, this promotes angiogenesis (the formation of new blood vessels), growth factor and cytokine synthesis, cell proliferation and differentiation, collagen production, and tissue repair, while also reducing inflammation and fluid buildup (edema) that can cause swelling at the wound site [22]. Excessive NO binding can be detrimental to cellular respiration because it competes with oxygen for COX binding. PBM facilitates the photodissociation of NO from COX, improving cellular respiration.

Photobiomodulation and Diabetic Complications

PBM has emerged as an alternative treatment for diabetic complications, and red and NIR light has shown stimulatory effects in enhancing wound healing, alleviating pain, and reducing inflammation [9]. The use of blue light has demonstrated antimicrobial effects, thereby reducing wound infections and maintaining wound bed sterility [13]. High blood sugar in diabetic patients causes several complications, as shown in Fig. 3. Diabetic eye disease (DED) encompasses a range of eye disorders, such as diabetic macular edema (DME), diabetic retinopathy (DR), and glaucoma [23]. Damaged blood vessels in the retina result in DR. In the kidneys, diabetic patients suffer from chronic kidney disease (CKD) or diabetic kidney disease (DKD) as a result of diabetic nephropathy and other related conditions such as hypertension, relapsing urinary tract infections, polyneuropathic bladder dysfunction, or macrovascular angiopathy. Nerve damage results in numbness, tingling, and reduced pain perception, leading to diabetic neuropathy (DN). Peripheral neuropathy affects the distal nerves of the limbs and, together with peripheral vascular disease (PVD), facilitates the development of non-healing wounds and ulcers on the feet, better known as diabetic foot ulcers (DFUs) [24]. Heart attack and ischemic stroke can also occur due to cardiovascular diseases (CVD), such as diabetic cardiomyopathy and cerebrovascular dysfunction caused by chronic traumatic brain injuries and other brain-related complications.

Diabetic Wound Healing

Diabetic ulcers represent a significant health concern because they are unable to progress through the usual phases of healing within the expected time. The human body possesses a remarkable ability to heal and regenerate following injury and invasions by microorganisms [25]. When injured, the body initiates wound healing process with the aim of restoring structural integrity. This process involves four overlapping phases, namely hemostasis, inflammation, proliferation, and remodeling (Fig. 4). Typically, injury triggers hemostasis, enabling the formation of a blood clot or platelet plug that stops bleeding through the deposition of fibrin. Within hours of injury, the inflammatory phase starts and is characterized by the presence of inflammatory cells, including neutrophils, lymphocytes, and macrophages, that migrate to and infiltrate the wound, acting to clear away debris and prevent microbial invasion [26]. Afterwards, the proliferation phase ensues, during which new tissue, such as blood vessels, is formed and collagen and extracellular matrix (ECM) are produced by fibroblasts - cellular events that are critical for wound structure and support. During the last stage of wound healing, the newly developed connective tissue undergoes remodeling and maturation, resulting in scar formation. In diabetic patients, the wound healing process is dysregulated due to a persistent inflammatory phase, and frequently results in ulcers that become chronic and difficult to heal, known as DFUs [19].

Between 40 and 60 million people worldwide suffer from DFUs, a common complication of diabetes that frequently results in severe infections and amputations [27]. Various studies have examined the effects of different wavelengths on DFUs using LEDs and laser light [28–39]. In a recent clinical study [28], PBM (904 nm, 70 mW, 1 W/cm^2) reduced DFU size across all tested energy densities (4, 8 and 10 J/cm^2). While all energy densities were effective, 10 J/cm^2 demonstrated the greatest improvement [28]. Similar healing effects were reported in a clinical trial using a combination of infrared (904 nm, 20 mW, 40 mW/cm^2, and 6 J/cm^2) and red (635 nm, 20 mW, 15 mW/cm^2, and 5 J/cm^2) light [29]. PBM has been shown to be beneficial for pain relief and wound closure in diabetic patients [30–32]. Esmael *et al*. [33] investigated the effect of red (650 nm) and combined red and infrared (810, 980, 915, and 650 nm) laser light with fluence (energy density) ranges of 4–10 J/cm^2 and an average power output of 4 W on chronic DFU healing in patients. The results showed that the combination of red and infrared lasers used in a sequential mode stimulated fibroblast growth, collagen production, angiogenesis, and wound re-epithelialization [33]. Cai *et al*. [34] examined the effects of combined red (630 $\pm$ 10 nm) and blue (460 $\pm$ 10 nm) wavelengths using LED lamps at 4.8 J/cm^2 and an average power output of 1.04 W on diabetic wounded rats and endothelial cell models, which increased overall wound cell migration rate, cell viability, and prolif-

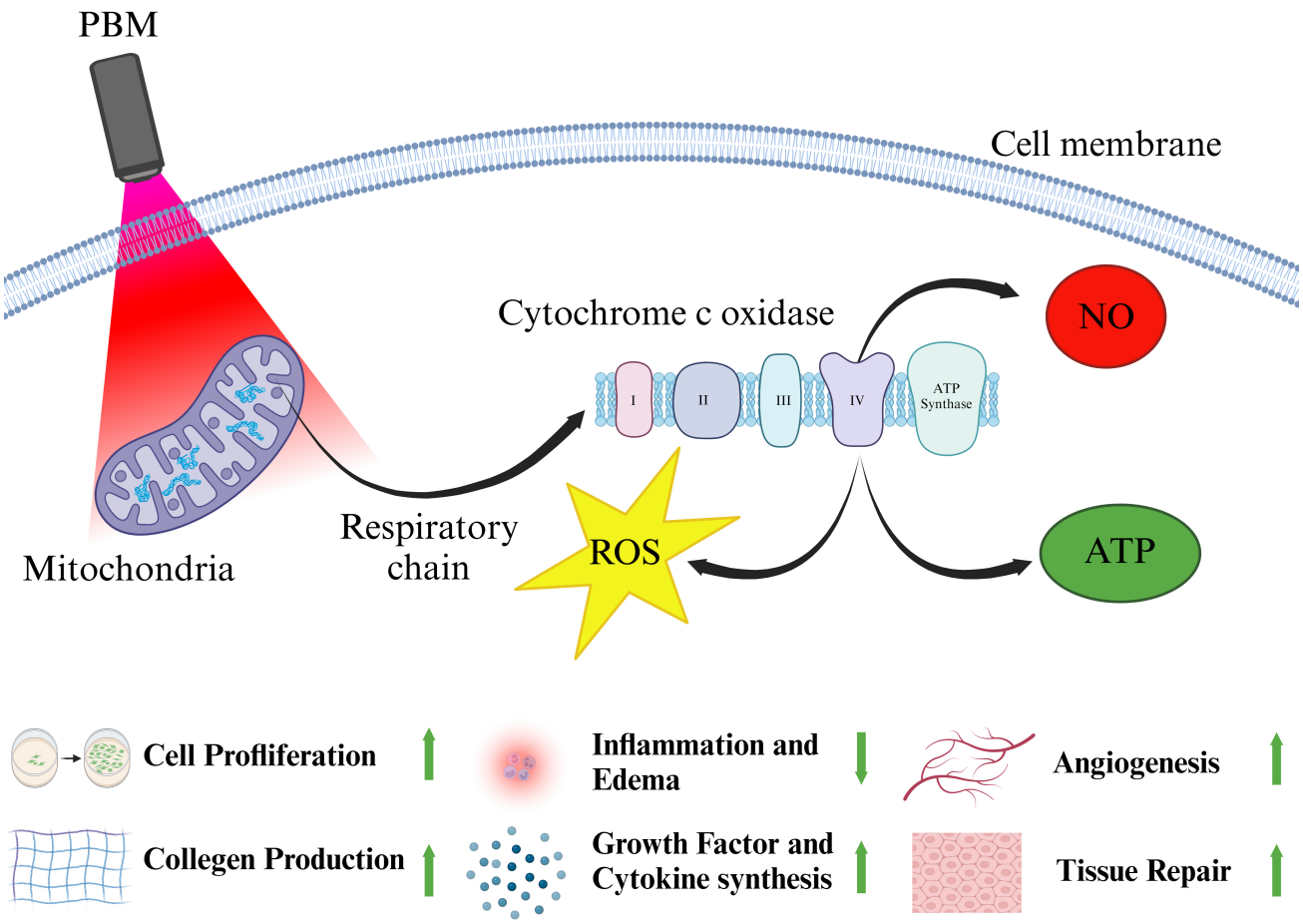

Fig. 2. Schematic overview of photobiomodulation (PBM) mechanism. The mechanism of action of PBM involves the absorption of photons by the mitochondria, which leads to a series of biochemical reactions. Light is specifically absorbed by cytochrome c oxidase (COX) of the mitochondrial respiratory chain (complex IV). Photon absorption triggers the dissociation of nitric oxide (NO), along with the synthesis of reactive oxygen species (ROS) and adenosine triphosphate (ATP), both of which are important for cellular functioning. These biochemical changes lead to cellular changes. Created with BioRender.com.

eration. The treatment accelerated wound healing through increased NO and collagen deposition, and reduced inflammation and ROS production [34]. PBM (808 nm) at various power outputs (0.1 W, 0.2 W, and 0.3 W), power densities (0.1 W/cm^2, 0.2 W/cm^2, and 0.3 W/cm^2) and irradiation times (17 s, 25 s, and 50 s) at 5 J/cm^{2}was used on streptozotocin-induced diabetic rat wounds [35]. Low power densities enhanced wound healing compared to high power densities that slowed down healing [35]. *In vitro* studies have shown that PBM using red and NIR wavelengths at 4–10 J/cm^2 positively influences diabetic wounds in human fibroblast cells by significantly increasing wound contraction and reduction [33,34,36–38]. PBM using LED blue light (420–485 nm) at different energy densities (3–55 J/cm^2) has been shown to promote wound healing in human fibroblast and keratinocyte cells. The effectiveness of the treatment varied in cell types and energy densities [15,16]. Although LED blue light (470 nm, 1 W, 50 mW/cm^2) has been reported to decrease wound size in an excision wound model in rats during a 5-day illumination period [17], the same wavelength (470 nm), with 14.4 J/cm^2 and 40 mW/cm^2, was found ineffective on a murine excision wound model over a period of 24 days [39]. Differences in treatment outcomes may be linked to varying PBM treatment plans, especially the frequency and length of treatment sessions. Precise treatment duration is crucial for optimizing the treatment's benefits, while preventing ineffective or harmful overexposure. Further research is needed to optimize PBM parameters and to understand the biochemical mechanisms of action involved in the treatments.

Diabetic Eye Disease

DED is characterized by a group of eye complications that can occur in diabetic patients, such as DR and DME [23]. DR is widely divided into two classes: proliferative diabetic retinopathy (PDR), an advanced stage characterized by the retina's dysfunctional development of blood vessels, and non-proliferative diabetic retinopathy (NPDR).

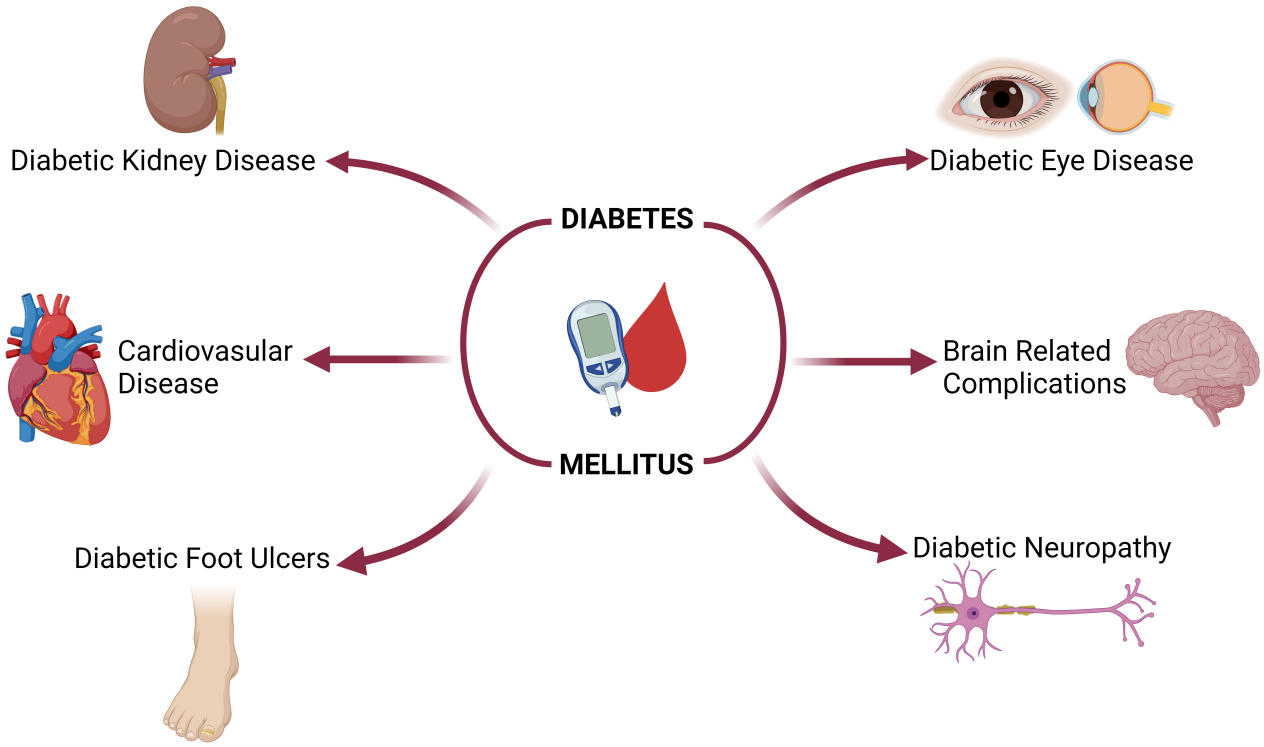

Fig. 3. Schematic overview of diabetic complications. Diabetes-related complications can impact a patient's brain, heart, and feet (macrovascular complications), as well as the eyes, kidneys, and nerves (microvascular complications). Created with BioRender.com.

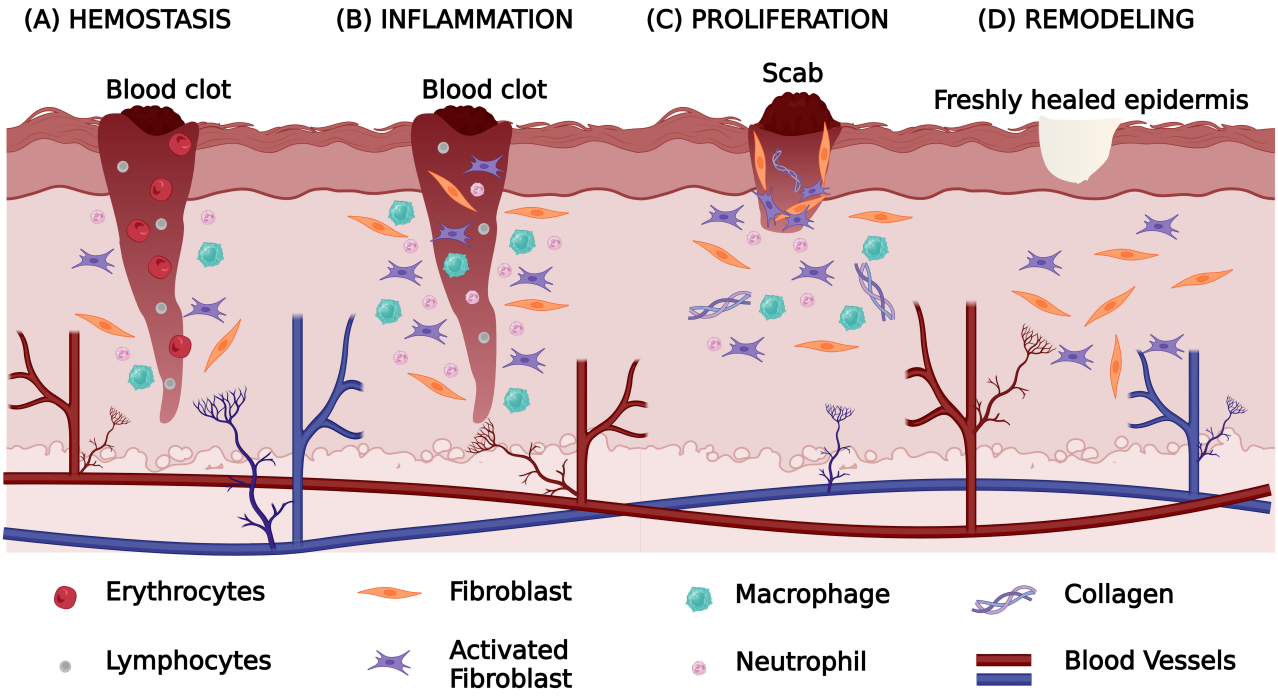

Fig. 4. Schematic diagram outlining the phases of wound healing. Hemostasis (A), inflammation (B), proliferation (C), and remodeling (D). Created with BioRender.com.

These vessels may break, causing leakage into the central retina (macular edema), leading to DME and related hemorrhagic complications. Globally, 103 million people were affected by DR in 2020, and the figure is projected to increase to 161 million by 2045 [40]. Hyperglycemia in diabetic patients can further lead to structural damage in

the optic nerves, resulting in glaucoma. PBM treatment at 670 nm, 20.25–25 mW/cm^2, 200–240 s and 5 J/cm^2 on diabetic mice prevented the decrease in visual function, increased vascular permeability, and capillary regression caused by diabetes through the reduction of retinal ganglion cell (RGC) death, inflammation, oxidative stress, and superoxide production, improving retinal calcium channel function and electroretinogram (ERG) amplitude [41–43]. Consistent with this, in cell culture models, PBM treatment (670 nm, 25 mW/cm^2, 180 and 80 s, 4.5 and 25 J/cm^2) reduced the production of pro-inflammatory mediators and ROS, and preserved mitochondrial integrity and ATP production [44]. Clinical studies have shown that daily PBM treatment at 670 nm (25–500 mW/cm^2, 4.53 and 25 J/cm^2) for 2–9 months significantly reduces microvascular leakage and central retinal thickness during DME, suggesting better PBM outcomes in DED [44–46]. Nonarath *et al*. [47] reported that PBM using an LED array (670 nm, 25 mW/cm^2, 180 s and 4.5 J/cm^2) decreased oxidative stress and cell death in rat Müller glial cells cultured in 30 mM glucose. A similar finding was reported on retinal cells grown in 25 mM glucose exposed to 670 nm, 25 mW/cm^2, 200 s and 5 J/cm^2 [43]. Altogether, PBM studies at 670 nm, 25 mW/cm^2, and energy density within the 4.5–25 J/cm^2 range have demonstrated therapeutic effects, and this wavelength is likely to be the most effective in eye-related complications in diabetic patients. Optimal light intensity, or power density, is crucial for stimulating cellular activity without causing tissue damage or overheating. Finding the right balance is essential for successful treatment outcomes. A patent by Tedford *et al*. [48] exploring the use of non-invasive multi-wavelength (630–1000 nm) PBM for acute and chronic ocular injuries or disorders, including DR and glaucoma, further confirmed the use of LEDs at 670 nm wavelength in accelerating retinal healing and enhancing visual acuity. Recently, PBM treatments using wearable devices for ocular treatments have been extensively explored in the red and NIR electromagnetic spectrum [49–52].

Diabetic Neuropathy

DN is characterized by neuronal dysfunction caused by nerve damage, muscle weakness, and sensory deficits resulting from diabetes. Patients with DN often have a high risk of developing DFUs and, subsequently, amputation [24]. While the exact worldwide rate of diabetic peripheral neuropathy (DPN) is uncertain, available data suggests a prevalence ranging from 22% to 46.5% in Latin America and the Caribbean, with even higher rates of 22% to 66% in Africa, and 52.2% to 53.6% in Ethiopia [53–55]. PBM has demonstrated positive neuroprotective effects by enhancing nerve regeneration and conduction velocity, and reducing neuropathic pain and inflammation. Clinical studies have demonstrated using PBM can reverse pain sensation and improve the quality of life in patients with DN [56–58]. PBM (630 and 810 nm, 35 mW/cm^2, 32.08 J/cm^2, 0.196 cm^2, 15 min) has been demonstrated to alleviate symptoms of DN without causing any adverse effects in patients with DPN [59]. Additionally, a significant reduction in serum neuron-specific enolase (NSE), a biomarker of neuronal damage, was reported in patients with DPN after a four-week treatment of PBM (632.8 nm, 660 nm, and 850 nm, 3.1 J/cm^2, 9 min) [60]. da Silva Oliveira *et al*. [61] utilized red light at 660 nm (1.6 J/cm^2) to explore the effects of glucose neurotoxicity on a mouse neuroblastoma cell line, resulting in increased cellular viability and stimulated neurogenesis. In streptozotocin-induced diabetic rats, PBM (660 nm, 30 mW, 1.6 J/cm^2, 0.28 cm^2, 15 s) has been shown to improve mitochondrial functionality and nerve damage after 21 consecutive applications [62]. Positive biomodulative effects, such as reversal of mitochondrial dysfunction and restoration of protein expression, using NIR light at 904 nm were observed against functional, molecular, and cellular alterations associated with nervous system destruction in DN [63–65]. Karkada *et al*. [66] reported on PBM treatments (665 and 808 nm, 2.64 and 120 mW/cm^2, 24 and 120 mW, and 4 J/cm^2) that improved oxidative status, cellular proliferation, keratinization, and epithelialization, all facilitating faster healing. Consistent with this, PBM with the same treatment parameters as in the aforementioned study, at fluences of 4, 6, and 8 J/cm^2, improved wound healing by stimulating accelerated wound contraction and resulted in a reduction of diabetic neuropathic ulcers [67]. Treatment with fluences of 10, 12, and 15 J/cm^2 resulted in a slower rate of wound reduction [67]. These studies used the same wavelengths, but different results were obtained at different fluences. This highlights the impact of different PBM parameters, and the need for further studies and optimization.

Diabetic Kidney Disease (DKD)

DKD is characterized by increased excretion of albumin in the urine and declining kidney function resulting from hyperglycemia-induced oxidative stress and inflammation [68]. According to the most recent report by the International Diabetes Federation (IDF), there was a 74% global increase in new cases of type 2 diabetes-related CKD between 1990 and 2017, rising from about 1.4 million to 2.4 million cases [69]. DKD advances through multiple stages, starting with microalbuminuria and advancing to macroalbuminuria, which is associated with renal disease progression and cardiovascular events [70]. Therefore, patients with DKD are most likely to develop CVD, which leads to heart attacks and ischemic strokes. Asghari *et al*. [71] investigated the effects of PBM at a wavelength of 685 nm, 15 mW and 3.2 J/cm^2 at six points on renal damage induced by ischemia/reperfusion in diabetic rats. The results showed that PBM at this wavelength mitigated kidney injuries and enhanced the antioxidant defense system [71]. PBM at 670 nm (10.5 J/cm^2, 35 mW/cm^2) has been demonstrated to in-

crease the activity of crucial enzymes such as COX and the antioxidant enzyme catalase (CAT), suppress DNA adduct formation, and reduce serum levels of blood urea nitrogen (BUN) and creatinine (Cr), thereby improving renal function in streptozotocin-induced diabetic rats [72]. PBM (810 nm, 6.9 W/cm^2, 200 mW and 206.9 J/cm^2) has also been utilized in closely related conditions such as chronic kidney failure or disease, exerting PBM-associated renoprotective effects, including enhanced functional capacity and muscle strength, which are characterized by reduced inflammation, oxidative stress, and kidney fibrosis [73].

Brain-Related Complications

Diabetes-induced hyperglycemia disrupts mitochondrial energy metabolism and augments oxidative stress, resulting in various brain disorders and neurodegenerative diseases such as depression, anxiety, cognitive impairment, and Alzheimer's disease (AD). Recently, increasing attention has been paid to shared characteristics of DT2 and the risk of developing AD, giving rise to diabetes type 3 (DT3), also known as diabetes of the brain [74]. DT3 occurs when peripheral insulin resistance triggers insulin in the brain, impacting gene expression, energy generation, and neuronal survival. Research has demonstrated that PBM using NIR irradiation (905 nm, 3000 Hz, 50 mW/cm^2, 3 J/cm^2) can pass through the scalp and skull to reach the superficial layers of the cerebral cortex, regulating neurobiological activity and delaying the prognosis of acute stroke [75]. Additionally, PBM (810 nm, 60 mW, 24 mW/cm^2) using an LED helmet has been shown to significantly enhance oxygen levels in the brain [76].

Interestingly, Correia Rocha *et al.* [77] investigated the effects of PBM using a pulsed gallium-arsenide laser (904 nm, 6.23 J/cm^2, 9500 Hz) on the anterior cingulate cortex of streptozotocin-induced diabetic rats that developed signs of DN, and their results suggested that the treatment may have modulatory effects on supraspinal brain regions. Horner *et al.* [78] demonstrated that a ketogenic diet and transcranial PBM (810 nm, 40 Hz, 240 J/cm^2) restores mitochondrial function, resulting in enhanced metabolic flexibility, elevated insulin sensitivity, and improved cognitive function in a diabetic patient with moderate AD. These findings are of clinical relevance, as PBM (635 nm and 810 nm, 10 Hz) using a home transcranial helmet, body pads, and an intranasal LED device has been shown to improve cognitive abilities, working memory, and quality of life in patients with AD [79]. Transcranial PBM can improve mitochondrial function in the brain by enhancing energy metabolism through increased cerebral oxygenation, ATP production, and NO release, especially in older individuals [80]. There is a significant discrepancy in both red and NIR PBM energy density levels across studies investigating diabetes-related brain complications, emphasizing the need for more research to provide comprehensive insights and clarity to address the discrepancy. This parameter is crucial as it determines the amount of light energy delivered to cells, which must be sufficient to induce the intended biological response.

PBM Limitations and Future Studies

Understanding the impact of blue, red, and NIR PBM wavelengths on various diabetic complications is crucial for healthcare professionals, researchers, and patients. The lack of broad consensus regarding wavelength, radiation exposure parameters, treatment duration, and administration mode when treating specific diabetic complications hampers the clinical adoption of PBM. Establishing specific parameters for PBM in experimental studies, followed by validation in more extensive clinical trials, is needed to guide its successful implementation. This may provide clinicians with a new tool to optimize treatments and improve diabetic patients' quality of life by promoting the timely healing and prevention of severe complications like amputations. Some researchers have broadened their study designs to take into account additional elements that affect the therapeutic effects of PBM by using different energy doses, light sources, and multiple or combined wavelengths in one experiment. Individual patient reactions to PBM may vary across clinical studies, and not all patients may achieve the same level of recovery or symptom reduction. In addition, owing to the heterogeneity of diabetic complications, patient age, general health status, and genetic variations, it can be challenging to anticipate a patient's response to PBM [45,46,59,74,80,81]. The clinical usefulness of PBM is also constrained by the lengthy PBM treatment cycle, as observed in studies on eye complications [41,42]. More research can be conducted on optimizing PBM parameters to reduce treatment duration cycles. Due to poor patient adherence to treatment in clinical research, our knowledge of the long-term effects of PBM remains limited. Besides, research progress concerning PBM treatment for internal organs such as the kidney has been inconspicuous, mainly due to anatomical hindrance. Therefore, further research is warranted to maximize the clinical potential of PBM. Future studies could explore the use of optical fibers for delivering light to internal organs during PBM treatment.

Conclusion

Considering the studies highlighted in this review, PBM is effective in regulating diabetic neuropathic and nephropathic symptoms and other brain-related complications using the red and NIR light, which can also be used to treat diabetic patients with lower limb neuropathies, thereby reducing the risk of amputations. The use of PBM with blue light wavelengths has not been widely explored in most diabetic complications, as it does not have a deep penetration depth, potentially hindering its treatment efficiency in clinical studies. However, positive healing effects have been observed in response to the use of blue light com-

bined with red/NIR light. Blue light can be used to treat infected wounds, something that should be more closely studied with the increase in antibiotic microbial resistance. Wavelengths outside the therapeutic window are not frequently used in PBM due to their lower effectiveness, and more studies are needed to determine their effects. Indeed, PBM offers a potentially effective, safe, and noninvasive therapeutic option for individuals with diabetic complications. However, further research is needed to optimize its parameters and dissect its mechanisms of action, with the major aim to expedite healing and abrogate severe diabetic complications. Investigating the potential benefits of combining PBM with complementary modalities, such as ultrasound or magnetic fields, to enhance light penetration and improve therapeutic outcomes in diabetic complications, particularly those affecting deep tissues like the brain and kidneys, represents a promising avenue for future research.

Abbreviations

AD, Alzheimer's disease; ATP, adenosine triphosphate; CVD, cardiovascular diseases; BUN, blood urea nitrogen; CAT, catalase; CKD, chronic kidney disease; COX, cytochrome c oxidase; Cr, creatinine; DED, diabetic eye disease; DFUs, diabetic foot ulcers; DKD, diabetic kidney disease; DME, diabetic macular edema; DM, diabetes mellitus; DN, diabetic neuropathy; DPN, diabetic peripheral neuropathy; DR, diabetic retinopathy; ECM, extracellular matrix; ERG, electroretinogram; IR, infrared; LEDs, light-emitting diodes; LLLT, low-level laser therapy; NIR, near-infrared; NO, nitric oxide; NPDR, non-proliferative diabetic retinopathy; NSE, neuron-specific enolase; MMP, mitochondrial membrane potential; PBM, photobiomodulation; PDR, proliferative diabetic retinopathy; PVD, peripheral vascular disease; RGC, retinal ganglion cell; ROS, reactive oxygen species; UV, ultraviolet.

Availability of Data and Materials

Not applicable.

Author Contributions

LH, conceptualization, data curation, writing original draft, and writing-review and editing; NNH, conceptualization, writing-review and editing, supervision, and funding acquisition. Both authors contributed significantly to editorial changes of important content. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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