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EDITED BY
Marcelo Victor Pires de Sousa,
D'Or Institute for Research and Education (IDOR), Brazil

REVIEWED BY
John LaRocco,
The Ohio State University, United States
Afshan Shirkavand,
Tehran University of Medical Sciences, Iran

*CORRESPONDENCE
Marucia Chacur,
chacurm@icb.usp.br

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Photobiomodulation therapy in neuropathic pain: mechanisms, evidence, and future directions

Daniel O. Martins[1], Igor R. C. Rocha[2,3], Linda R. Watkins[3] and Marucia Chacur[2,4]*

[1]Laboratory of Neuroscience, Hospital Sírio-Libanês, São Paulo, Brazil, [2]Department of Anatomy, Institute of Biomedical Science, University of Sao Paulo, São Paulo, Brazil, [3]Department of Psychology and Neuroscience, and the Center for Neuroscience, University of Colorado, Boulder, CO, United States, [4]Neuroscience and Behavior, Institute of Psychology, University of Sao Paulo, São Paulo, Brazil

Neuropathic pain (NP) is a chronic and disabling condition resulting from injury or disease of the somatosensory system. Characterized by sensory disturbances such as allodynia, hyperalgesia, and spontaneous pain, NP remains a major clinical challenge due to the limited efficacy and significant side effects of conventional pharmacological treatments. In recent years, photobiomodulation therapy (PBMT), also referred to as low-level laser therapy (LLLT), has emerged as a promising non-pharmacological strategy for managing NP. PBMT involves the application of red or near-infrared light to biological tissues, triggering a range of photochemical and photophysical responses that enhance mitochondrial function, reduce oxidative stress, modulate inflammation, and support neural repair. This review provides a comprehensive synthesis of the current evidence on PBMT for NP, integrating mechanistic insights with preclinical findings. We discuss the biological underpinnings of PBMT, including mitochondrial activation via cytochrome c oxidase, modulation of cytokines and oxidative stress markers, and upregulation of neurotrophic factors such as BDNF. Preclinical studies in well-established NP models (e.g., chronic constriction injury, spared nerve injury, diabetic neuropathy) demonstrate consistent analgesic effects and neuroprotective outcomes following both local and remote/systemic PBMT applications. We also highlight key limitations and knowledge gaps in the field, including the need for standardized protocols, greater exploration of remote PBMT strategies, and improved consideration of sex-based responses. Finally, we outline future directions, such as integration with multimodal therapies, personalized dosimetry, and the development of wearable and transcranial PBMT technologies. Together, the existing body of evidence supports PBMT as a safe and potentially effective tool for NP management, while underscoring the need for more rigorous and translational research.

KEYWORDS

photobiomodulation therapy, neuropathic pain, translational models, clinical applications, therapeutic parameters

1 Introduction

Neuropathic pain (NP) is a complex and debilitating chronic condition resulting from damage or disease affecting the somatosensory nervous system. It is characterized by a range of sensory abnormalities, including allodynia, hyperalgesia, and spontaneous pain. Epidemiological data indicate that NP affects approximately 6%–10% of the general population, with profound consequences on sleep quality, emotional wellbeing, functional capacity, and overall quality of life (Colloca et al., 2017).

1.1 Clinical challenges and limitations of current treatments

Despite the availability of several pharmacological options, the effective management of NP remains a significant clinical challenge. First-line treatments, including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), and anticonvulsants such as gabapentinoids, often yield only partial pain relief, with less than 50% improvement reported in many patients (Finnerup et al., 2015). Moreover, these drugs are frequently associated with adverse effects, including sedation, dizziness, cognitive impairment, gastrointestinal disturbances, and, in the case of opioids, tolerance and dependence (Dworkin et al., 2010). Such limitations underscore an urgent need for safer and more effective non-pharmacological or adjunctive therapies.

1.2 The emergence of photobiomodulation therapy (PBMT)

Among the emerging non-pharmacological strategies, PBMT, also known as low-level laser therapy (LLLT), has gained considerable attention for its potential role in NP management. PBMT involves the application of low-intensity red or near-infrared light (typically 600–1,070 nm) to target tissues, leading to photochemical and photophysical effects at the cellular level (Hamblin, 2016). Mechanistically, PBMT modulates mitochondrial function enhancing ATP production, reducing oxidative stress, and stimulating nitric oxide (NO) release while also influencing inflammatory cascades and neuroimmune responses (Hamblin, 2017; Yang et al., 2020).

Due to PBMT's role in modulating cell signaling and function, there has been considerable interest in using PBMT to treat a wide range of disorders. It has been successfully applied in preclinical studies to optimize treatment protocols.

Preclinical studies using well-established models of NP, such as chronic constriction injury (CCI) and diabetic peripheral neuropathy (DPN), have demonstrated that PBMT reduces mechanical and thermal hypersensitivity, suppresses pro-inflammatory cytokines (e.g., TNF-α, IL-1β), downregulates MAPK signaling pathways in dorsal root ganglia, and promotes neuroprotection and tissue repair (de Oliveira Martins et al., 2013; de Freitas and Hamblin, 2016; Martins et al., 2017a; Martins et al., 2017b; Oliveira et al., 2017; Rocha et al., 2017; Martins et al., 2020; Rocha et al., 2021; Marques et al., 2023; Chacur et al., 2024; Ferreira et al., 2024; Martins et al., 2024).

1.3 Clinical evidence supporting PBMT for neuropathic pain

The therapeutic promise of PBMT has extended into clinical settings. Randomized controlled trials (RCTs) and observational studies have reported beneficial effects in patients with various NP conditions, including diabetic peripheral neuropathy (Kumar et al., 2015; Korada et al., 2023), chemotherapy-induced peripheral neuropathy (Argenta et al., 2017). Observed outcomes include significant reductions in pain intensity, improvements in nerve conduction velocity, and enhanced patient-reported quality of life, all with minimal adverse events (Mortazavi et al., 2002).

Nevertheless, the translation of PBMT into routine clinical practice for NP is still limited. A major barrier lies in the heterogeneity of study designs, variability in laser parameters (e.g., wavelength, energy density, pulse mode, treatment frequency), small sample sizes, and inconsistent outcome measures across trials. This variability hampers the development of standardized, evidence-based clinical protocols.

This review aims to provide a comprehensive and critical analysis of the current state of knowledge regarding PBMT in the management of NP. It will focus on elucidating the underlying biological mechanisms, evaluating preclinical evidence, and identifying methodological gaps that need to be addressed. By integrating mechanistic insights with clinical findings, this work seeks to contribute to the translational advancement of PBMT and support the development of more effective, safe, and accessible strategies for NP management.

For this narrative review, we conducted a comprehensive search in PubMed, Scopus, and Web of Science, for potentially eligible studies published in English, the following search terms were employed: "photobiomodulation, low-level laser therapy, neuropathic pain, nerve injury, inflammation, mitochondria, and glial activation". The search covered studies published between 2000 and 2025, with earlier seminal papers included when relevant. Duplicate articles were removed. Preclinical and clinical studies exploring PBMT mechanisms, neuropathic pain models, molecular outcomes, and translational findings were considered, while studies unrelated to pain or using non-PBMT phototherapies were excluded. This approach ensured a coherent and focused selection of literature while maintaining the narrative structure of this review.

2 Neuropathic pain: pathophysiology and challenges

Illnesses such as autoimmune diseases (multiple sclerosis), metabolic diseases (diabetic neuropathy), infections (shingles, postherpetic neuralgia), vascular disease (stroke), trauma, and cancer can cause lesions to the nervous system, thus leading to NP (Campbell and Meyer, 2006; Oaklander, 2008; Schreiber et al., 2015; Treister et al., 2017; Yoon and Oh, 2018). Although there is a rule without evident exception that those lesions that lead to NP must involve the nociceptive pathways (Boivie et al., 1989), not all lesions of the nociceptive pathways induce pain. For example, lesions of the medial lemniscus system (e.g., dorsal columns) do not induce pain (Cook and Browder, 1965). Despite numerous

studies, the mechanisms of NP development and persistence remain unknown (Weihe et al., 1991; Woolf and Mannion, 1999; Mika et al., 2013). Studies involving gene expression suggest that NP might be associated with glial activation (Mika et al., 2013), cytokine signaling (Malcangio et al., 2013), and neuroplasticity (Jayathilake et al., 2025). Moreover, recent studies suggested a significant contribution of neuroimmune interactions in the loss of opioid analgesic efficacy (DeLeo and Yezierski, 2001; Watkins et al., 2003; Mika, 2008). Regardless of etiology, location and intensity, NP is characterized by alterations in the normal processing of sensory signals (Karavis et al., 2023) and despite the absence of identifiable tissue damage, NP is maintained through the development of peripheral and central maladaptive mechanisms (Karavis et al., 2023; Meacham et al., 2017).

Besides structural, metabolic, and functional support to neurons (Susuki, 2010; Rasband, 2016; Barros et al., 2018), neuroglial cells such as microglia, astrocytes, oligodendrocytes, and ependymal cells, actively participate in the reception, transmission, processing, and modification of neural responsivity (Karavis et al., 2023). Microglial cells in the central nervous system (CNS) quickly respond with morphological and functional changes when stimuli affect physiological homeostasis in the CNS (Xavier et al., 2014; Colonna and Butovsky, 2017; Augusto-Oliveira et al., 2025). For example, pain stimuli and nerve injury increase microglial numbers and activation, presenting spectrum of phenotypes, from pro-inflammatory (i.e., M1-type) through to anti-inflammatory (i.e., M2-type) (Lin et al., 2007; Chen et al., 2018; Barcelon et al., 2019; Tu et al., 2021; Wu et al., 2023). Furthermore, microglial cells and the immune system through cytokines signaling have substantial contribution for the development and maintenance of NP (Malcangio et al., 2013; Sommer and Schäfers, 2004; Hung et al., 2017; Tsujikawa et al., 2023). Moreover, there are many mechanisms by which microglial cells might initiate and maintain NP. After nerve damage or inflammation, microglia can recognize pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), thus triggering their activation (Kofler and Wiley, 2011). Furthermore, microglia can also contribute to pain after neural release of caspase 6, as caspase six triggers microglial release of tumor necrosis factor-alpha (TNFα), a key contributor to NP (Leung and Cahill, 2010; Berta et al., 2014).

Although glial cells are key components to neuropathic pain development and maintenance (Gwak et al., 2017), another player might be involved in that role as well. NP is maintained and intensified through complex neuro-glial interactions, where the activation and subsequent functional changes - including but not limited to morphological alterations (microgliosis) - of glial cells (microglia, astrocytes, and satellite glial cells) are critical, alongside the concurrent dysregulation of neurons and the involvement of other non-neuronal immune cells (Karavis et al., 2023; Beggs and Salter, 2010; Gosselin et al., 2010; Jha et al., 2012).

Recent findings suggest that neural plasticity in the brain is a relevant component for the development and maintenance of NP (Costigan et al., 2009; Hiraga et al., 2022). Neural plasticity can be defined as functional and structural changes in neurons (Bak et al., 2021). Neuronal functional changes can include alternations in calcium activity, excitatory postsynaptic current (EPSC) frequency, EPSC amplitude, intrinsic excitability, synaptic strength, and brain oscillations (Bak et al., 2021; Sarnthein et al., 2006; Kuner and Flor, 2017; Zhuo, 2019). In contrast, neural structural alterations include increased density of dendritic spines in the primary somatosensory cortex (S1) and in the anterior cingulate cortex (ACC) and gain of presynaptic axonal boutons in S1 (Colloca et al., 2017; Bak et al., 2021; Sarnthein et al., 2006; Zhuo, 2007). According to Sun Kwang Kim et al., these changes can serve as biomarkers for NP (Bak et al., 2021). Furthermore, recent evidence has showed that reversal of neural plasticity leads to analgesic effects (Jayathilake et al., 2025).

Despite enormous progress in understanding both acute and chronic pain basic mechanisms (Gregory et al., 2013), pain is still a challenging burden to treat, and few basic science advances have been effectively translated to the clinical setting over the last several decades (Gregory et al., 2013). Although animal models for pain studies have been pivotal in the understanding of pain processes (Deuis et al., 2017), pain is a heterogenous phenomenon that broadly differs based on the affected tissue and the mechanism of injury (Ness and Gebhart, 1990; Sluka, 2002; DeSantana and Sluka, 2008; Milligan and Watkins, 2009; National Research Council US, 2009; Haroun et al., 2023). Animal pain models that quantify reflexive behaviors such as withdrawal thresholds to an applied noxious and non-noxious stimuli have been used for decades and have increased our knowledge and understanding of the basic mechanisms of pain processing, including structure and physiology of nociceptors, and identification of neurotransmitters, receptors, intracellular messengers, and genes involved in pain behaviors (Gregory et al., 2013). Moreover, animal pain models have expanded our comprehension of existing pharmacological and non-pharmacological pain treatments (Joshi and Honore, 2006). Furthermore, despite all the knowledge gained from animal pain models, effective pharmacological approaches to treat pain is still widely considered to be lacking, particularly for chronic pain including NP (Tennant, 2016; Fornasari, 2017), paving the way for non-pharmacological approaches to treat pain.

3 Photobiomodulation therapy (PBMT): principles and biological mechanisms

Photobiomodulation Therapy has received a lot of attention for its different roles, such as in tissue repair (Nair et al., 2023), alleviation of pain (Sfondrini et al., 2020), nerve stimulation (Rampazo et al., 2024), edema reduction (Hadad et al., 2022), modulate inflammatory processes (Li et al., 2020), and modulation of cellular metabolism and biomolecular pathways (Jere et al., 2022). PBMT acts by using monochromatic light energy, usually within red and near-infrared (NIR) wavelength regions (600–1,200 nm) (Gupta et al., 2014). PBMT utilizes low-power light sources like light amplification by stimulated emission of radiation (LASERs) or light-emitting diodes (LEDs) to promote specific effects in the target tissue. Light is a form of electromagnetic radiation that exhibits both wave-like and particle-like properties. It is defined by several characteristics, including energy, wavelength (the distance between two wave peaks), frequency, and amplitude. Energy is measured in joules (J), and the amount of energy delivered per unit of time determines the power of light, expressed in watts

(W = J/s). All these characteristics are essentials for beneficial biomodulatory effects of PBMT.

A laser produces light by exciting atoms or molecules, causing them to emit light at specific wavelengths. This light is then amplified to form a narrow, focused beam. When a photon with the appropriate energy passes through the laser medium, it can stimulate an excited atom to release another photon with the same energy, direction, and phase. This process generates an organized and uniform wave of light, known as coherent light (Svelto et al., 2007). For coherence to occur, more atoms must be in an excited state than in their resting state, a condition referred to as population inversion. Without population inversion, the light would be absorbed rather than amplified. To achieve this, an external energy source, such as intense light or an electric current, excites the atoms. Once a sufficient number of atoms are excited, the light is amplified through repeated stimulation. A pair of mirrors positioned at either end of the laser cavity helps build up the light energy. As the light reflects back and forth, it repeatedly passes through the laser medium, increasing in intensity. One of the mirrors allows a portion of the light to escape, producing the laser beam. This arrangement generates light that is coherent, monochromatic, and tightly focused (Karu and Simunovic, 2003).

LEDs are light sources based on the electroluminescence of semiconductor materials, most commonly InGaN (60%) and AlInGaP (38%) (Renk, 2012). LEDs are considerably less expensive than lasers, and PBMT using light-emitting diodes is a relatively recent development. Nevertheless, the use of LEDs in photobiomodulation and other healthcare applications is now well established, and their efficacy has been demonstrated in numerous reports (Tenis et al., 2018; Lin et al., 2020; Martins et al., 2022).

3.1 Key parameters: wavelength, dose, power, frequency, site of application

Laser light is characterized by four main properties: monochromaticity, coherence, directionality, and high intensity. These properties distinguish laser light from LEDs and conventional light sources (Jelínková and Šulc, 2013). Monochromaticity means that laser light consists of a single wavelength (measured in nanometers, nm), with the visible spectrum ranging from 380 to 780 nm and near-infrared from 600 to 1,200 nm. Coherence allows laser light to be focused to a very small spot (laser light is coherent, whereas LED light is incoherent) (Svelto et al., 2007). Directionality, or collimation, enables laser light to travel long distances with minimal spreading (Jelínková and Šulc, 2013). High intensity arises as a result of these intrinsic properties.

In addition to these optical properties, PBMT also involves fundamental treatment parameters. Energy density, expressed in J/cm^2, is a critical descriptor of the dose, representing the relationship between power and exposure time. Power density, in mW/cm^2, represents the power (in mW) divided by the irradiated area (in cm^2). Irradiation time, measured in seconds (s), is one of the most common time units. Pulse structure can be continuous wave (CW) or pulsed, with beams delivered as steady or pulsed waves. Moreover, PBMT outcomes depend on the treatment interval—hourly, daily, or weekly—since different intervals may produce distinct therapeutic effects (de Freitas and Hamblin, 2016; Zein et al., 2018).

Due to all these variations, the efficacy of PBMT remains a topic of debate. Further research is needed to study the diverse light parameters, especially irradiation patterns, and to elucidate their underlying molecular mechanisms of action.

Another essential consideration concerns optical intensity and the differences between laser and LED light sources. The biological response to PBMT is strongly influenced by irradiance (mW/cm^2) and fluence (J/cm^2), which follow a biphasic dose–response pattern in which both under- and over-irradiation can attenuate therapeutic effects. Although lasers generally achieve greater tissue penetration due to their coherence and beam collimation, LEDs can deliver comparable photobiomodulatory outcomes when intensity and dose parameters are matched, despite their broader and less collimated emission. Recent preclinical and clinical evidence supports the therapeutic potential of LEDs for superficial and moderately deep targets, whereas lasers may still be advantageous when higher irradiance at depth is required. Understanding these distinctions is essential for interpreting variability across PBMT studies and optimizing treatment protocols.

3.2 Cellular and molecular effects

The cellular effects of PBMT result from molecular changes involving signaling and effector molecules and transcription factors triggered by specific agents. Studies have reported various effects from low-power lasers and LEDs, such as changes in cell proliferation, viability, differentiation, apoptosis, and migration (Zecha et al., 2016; Dompe et al., 2020; Tam et al., 2020). For example, low-power green and infrared lasers have been shown to enhance the proliferation and viability of dental pulp stem cells and different types of fibroblasts, including diabetic and hypoxic diabetic wounded cells. Conversely, reduced viability was observed in oral squamous carcinoma and bladder cancer cells following exposure to low-power red, infrared, and blue lasers. Red LEDs were found to be more effective than infrared LEDs in promoting osteoblastic differentiation in periodontal ligament stem cells. Additionally, low-power lasers have been shown to influence stem cell differentiation and apoptosis, with some studies indicating increased apoptosis in certain tissues, while others reported a reduction in apoptosis markers under specific conditions.

The primary mechanism of LASER starts at cellular level, firstly by the interaction between light and cellular photoacceptors; i.e., mitochondria. In the inner mitochondrial membrane is the key initiating event for photobiomodulation particularly cytochrome c oxidase (CCO), which absorb the photons, promoting electron transport, increasing mitochondrial membrane potential, oxygen consumption, and ATP levels after PBMT (Hamblin, 2018). Both, LASER, and LED can activate CCO in mitochondria, resulting in a variety of biological responses, such as reducing inflammation, increasing ATP production, and regulating enzyme and gene expression (Cardoso et al., 2022a; Chamkouri et al., 2024; Zhang et al., 2024; Al Balah et al., 2025; Trajano et al., 2025).

Additionally, the biological effects of PBMT are wavelength-dependent, with different wavelengths (blue, green, red, and near-

TABLE 1 Wavelength-specific effects in photobiomodulation therapy.

Wavelength range	Primary cellular target(s)	Primary proposed mechanism	Main cellular/therapeutic effect	Tissue penetration
Red (~600–750 nm) (Hoh Kam and Mitrofanis, 2023; Kim et al., 2025)	Cytochrome c Oxidase (CCO) (Complex IV), Hemoglobin, Myoglobin	Photodissociation of inhibitory Nitric Oxide (NO) from CCO.	↑ ATP production, ↑ cell proliferation, ↓ inflammation, ↓ apoptosis	Moderate
Near-Infrared (NIR) (~750–1,200 nm) (Henderson, 2024; Nairuz et al., 2024; Shen et al., 2024)	Cytochrome c Oxidase (CCO)	Photodissociation of inhibitory Nitric Oxide (NO) from CCO.	↑ ATP production, neuroprotection, ↓ inflammation	Deepest (Optimal around 810 nm)
Blue (~400–500 nm) (De Lima et al., 2025; Stoelzle et al., 2003; Prado et al., 2023)	Heme groups (in Cytochromes, Hemoglobin), Flavins, Porphyrins	Induction of Oxidative Stress/Reactive Oxygen Species (ROS) (at higher doses) or NO release (at specific doses). Also, potentially light-gated Ca^{2+} channels	Antimicrobial, wound healing (superficial), potential for oxidative damage/apoptosis at high doses, stimulation of osteoblast differentiation	Shallowest
Green (~495–570 nm) (Soliman et al., 2024; Bao et al., 2025)	Unclear, potentially Light-gated Ca^{2+} channels	Activation of light-gated Ca^{2+} channels	↓Pain (visual exposure for migraine), stimulation of osteoblast differentiation	Shallow

infrared) engaging distinct primary photoacceptors, varying in tissue penetration, and eliciting different cellular responses. The red light range is a core component of traditional PBMT; but other visible light wavelengths like blue and green also have documented biological effects, often utilizing different mechanisms or chromophores (Serrage et al., 2019; Moradi et al., 2024).

Blue light (~400–500 nm) differs significantly in its mechanism and therapeutic window. Blue light is strongly absorbed by several biological molecules, particularly the heme groups in cytochromes and hemoglobin (due to the Soret band) and flavins. Blue light has the lowest tissue penetration due to high absorption by melanin and hemoglobin (Plavskii et al., 2018; Wu et al., 2018; Hui et al., 2025).

Green light (~495–570 nm) is the least studied but shows distinct effects. Like blue light, green light has a much lower tissue penetration than red/NIR light. Some research suggests that beneficial effects, particularly on stem cell differentiation (e.g., osteoblast differentiation), may be mediated by activation of light-gated Ca^{2+} channels, like blue light, rather than CCO activation (Fushimi et al., 2012; Catão et al., 2016; Simões et al., 2020) (Table 1).

When cells are exposed to red or near-infrared light, CCO absorbs the photon energy, leading to an electronic transition from a lower to a higher energy level in the chromophore. This process results in the release of an electron that contributes to cellular respiration and ATP synthesis. Consequently, PBMT may enhance the efficiency of cellular respiration by supporting cellular metabolism and increasing the cell membrane potential (Hamblin and Demidova, 2006). Retrograde mitochondrial signaling is one of the most common mechanisms involved in PBMT. Mitochondria can increase the mitochondrial membrane potential (MMP, $\Delta\Psi m$) by absorbing the energy of photons and altering the concentrations of ROS, NO, and calcium (Ca^{2+}), resulting in changes to the mitochondrial ultrastructure. These alterations lead to further changes in pH, ATP synthesis, cAMP levels, and intracellular redox potential (Ferraresi et al., 2015).

3.2.1 Anti-inflammatory actions (decreased proinflammatory TNF-α, IL-1β; increased anti-inflammatory IL-10)

The main regulators of the inflammatory response include TNF-α and proinflammatory interleukins, and changes in IL-6 and IL-1β levels are commonly used as indicators to evaluate treatment effects (Lee et al., 2017). PBMT treatments frequently focus on these proinflammatory cytokines to evaluate efficacy. PBMT using lasers or LED have been shown to reduce inflammation (Hamblin et al., 2017; Cardoso et al., 2022b), but likely due to different parameters have varying anti-inflammatory effects. Most of the studies show that PBMT inhibits the production of inflammatory factors such as TNF-α, IL-1β and IL-6 and upregulates anti-inflammatory factors such as, transforming growth factors-β (TGF-β) (Hamblin, 2017) and IL-10 (Martins et al., 2016). Ju and coworkers (2023) showed through transcriptome sequencing and bioinformatics analysis, the potential key pathways and genes involved in PBMT regulation of macrophage polarization, providing biological support for the clinical application of PBMT (Ju et al., 2023).

3.2.2 Antioxidant pathways (increased anti-inflammatory Nrf2, decreased pro-inflammatory ROS)

Decreases in ROS levels are among the most common effects of PBMT. While PBMT has the ability to induce a burst of ROS in normal cells, it is well documented that PBMT, when used therapeutically, can decrease markers of oxidative stress (Tatmatsu-Rocha et al., 2016; Karkada et al., 2022). Tomazoni and colleagues (2019) demonstrated that a PBMT protocol applied prior to exercise play an important antioxidant effect, increasing the activity of superoxide dismutase (SOD) and catalase (CAT), enzymes responsible for preventing oxidative damage (Tomazoni et al., 2019). To maintain redox homeostasis and prevent damage from redox-active species, the skin possesses an extensive network of antioxidant defense systems, primarily orchestrated by the nuclear factor erythroid-2-related factor 2 (Nrf2) pathway (Korkina and Pastore, 2009). It is well established that Nrf2 regulates the expression of a broad spectrum of antioxidant enzymes, such as superoxide dismutase (SOD) and glutamate-cysteine ligase catalytic subunit (GCLC); cytoprotective enzymes, including heme oxygenase 1 (HO-1); and phase II drug detoxification enzymes, such as NAD(P)H quinone oxidoreductase 1 (NQO1) (Baird and Yamamoto, 2020; He et al., 2020). To date, only a few studies have investigated the effects of

PBMT on Nrf2 expression and activity. Yadav and coworkers (2020) recently demonstrated activation of the Nrf2 antioxidant pathway associated with accelerated burn healing in mice treated with 904 nm PBMT (Yadav et al., 2020). However, there remains no strong evidence establishing a direct link between the therapeutic effects of PBMT and Nrf2 signaling during the inflammatory response.

3.2.3 Neural repair and neuroprotection (increased BDNF, modulation of glial cells)

Previous studies have shown that PBMT can improve neural repair by promoting nerve regeneration and functional recovery. PBMT has also been reported to induce neuroprotection, stimulate neurogenesis, and reduce cognitive dysfunction, making it a promising tool for modulating both CNS and PNS functions (Martins et al., 2024; Mortazavi et al., 2002; Yang et al., 2018; Zheng et al., 2021; Ma et al., 2022; Huang et al., 2023; Shirkavand et al., 2023). Brain-derived neurotrophic factor (BDNF), a neurotrophin that plays a crucial role in neuronal growth, survival, and differentiation, has been highlighted in this context (Lei et al., 2024). Studies demonstrate that PBMT positively influences the CNS by increasing BDNF synthesis (Heo et al., 2019; Lutfy et al., 2024; Zhang et al., 2025). Neuroinflammation, a process involving various cell types such as neurons and glial cells (including microglia and astrocytes) (Voet et al., 2019), can be simultaneously suppressed by PBMT, which also inhibits astrocyte proliferation (Tsai et al., 2022). These findings suggest that PBMT is a promising strategy for managing neuroinflammation, offering both neuroprotection and the alleviation of inflammation (Xie et al., 2023). Overall, the data provide evidence that PBMT may serve as an effective non-pharmacological intervention to reduce glial activation and pro-inflammatory cytokine expression.

4 Evidence from preclinical studies

A primary mechanism through which PBMT exerts its effects involves the activation of CCO, an essential enzyme in the mitochondrial respiratory chain (Ramanishankar et al., 2024). Photon absorption at wavelengths between 600 and 1,100 nm enhances enzymatic activity, increasing ATP production and transiently releasing NO, which in turn contributes to vasodilation and improved microcirculation (Hamblin et al., 2017; Karu, 1999; Poyton and Ball, 2011; Kashiwagi et al., 2023). This sequence of events boosts cellular metabolism, lowers oxidative stress, and initiates prosurvival signaling cascades.

In rodent models of NP (e.g., CCI, SNI), locally applied PBMT reliably reduces mechanical allodynia and thermal hyperalgesia, particularly in males (Rocha et al., 2021; Santos et al., 2018; Da Silva et al., 2019; Silva et al., 2019; de et al., 2020; Oliveira et al., 2020; Rocha et al., 2020; Canever et al., 2021; De Oliveira et al., 2021; De Brito et al., 2022; Pinto et al., 2022). These effects have been attributed to direct modulation of cells within the irradiated area, primarily neurons, Schwann cells, and immune cells, via enhanced mitochondrial function, reduced pro-inflammatory cytokines (IL-1β, IL-6), increased anti-inflammatory mediators (e.g., IL-10), and improved oxidative balance (Dompe et al., 2020; Hamblin, 2018; De Oliveira et al., 2021; Holanda et al., 2018; Sommer, 2020; Mazuqueli Pereira et al., 2021). These cellular effects are supported by *in vitro* data showing direct PBMT-induced changes in cytokine and ROS regulation (Funk et al., 1992; Funk et al., 1993). Studies also show that different wavelengths (e.g., 660 nm- Red vs. 980 nm - infrared) can yield distinct effects on both behavior and molecular signaling (Silva et al., 2019; Holanda et al., 2016; Castro et al., 2020; Balbinot et al., 2021; Correia Rocha and Chacur, 2021; Fuchs et al., 2021).

Despite clear evidence of systemic outcomes, the lack of systemic outcomes specifically focused on the female sex remains, as most clinical trials have been conducted in mixed populations or focused on males (Pereira et al., 2022; Pasternak-Mnich et al., 2024; Silva et al., 2025).

In contrast to PBMT applied directly to tissue injury or to cells in culture, virtually no animal studies have investigated systemic outcomes such as cytokine or mitochondrial markers in the blood or distant tissues following PBMT applied elsewhere. Remote PBMT, irradiation of body regions distant from the lesion, has shown behavioral efficacy in reducing pain, but studies are scarce and almost exclusively in male rodents (Hagiwara et al., 2008; Da Silva Oliveira et al., 2018; Tomé et al., 2020; Liebert et al., 2022; Wu et al., 2025). Remote effects are hypothesized to involve indirect mechanisms, including systemic mitochondrial signaling, modulation of circulating immune markers, or neuro-immune reflexes. Preliminary studies in both animals and humans (Huang YY. et al., 2012; Liebert et al., 2021; Silva and Pinheiro, 2021) suggest that remote PBMT can enhance clinical and behavioral recovery, reduce oxidative stress, and modulate systemic inflammation and neuroprotection, particularly in models of spinal cord injury, Parkinson's disease, and closed-head trauma (Tomé et al., 2020; Wu et al., 2025; Silva and Pinheiro, 2021; Huang SF. et al., 2012; Gordon and Johnstone, 2019; Johnstone et al., 2021; Oron et al., 2022). For instance, PBMT applied to the abdomen or limbs of human patients has been shown to improve mobility, cognition, and immune cell profiles and, in animal models, it has attenuated neurodegeneration in brain regions such as the substantia nigra and striatum (Wu et al., 2025; Gordon and Johnstone, 2019).

In addition to local and remote effects, PBMT may interact with other neuromodulatory modalities or present distinct advantages compared to them. Emerging studies suggest that combining PBMT with electrical stimulation, exercise, or magnetic stimulation could yield additive or synergistic effects, as these interventions share overlapping mechanisms related to mitochondrial enhancement, neuroimmune modulation, and analgesic neurotransmission. Furthermore, PBMT differs from other neuromodulation approaches (e.g., TMS, tDCS, peripheral electrical stimulation) by directly targeting mitochondrial chromophores, thereby influencing both neuronal and glial bioenergetics. These unique bioenergetic actions also raise the possibility of wavelength-dependent synergies, as different wavelengths penetrate tissue to varying depths and engage distinct cellular targets (de Freitas and Hamblin, 2016; Kocherova et al., 2021). Finally, stimulation site is another important determinant of PBMT effects: intranasal and auricular approaches may modulate cranial nerve pathways and systemic vascular responses, whereas forehead and temporal window irradiation can access cortical and subcortical circuits implicated in nociceptive processing. Despite these promising avenues, systematic head-to-head comparisons between PBMT delivery routes or between PBMT and other neuromodulation modalities

are virtually absent in neuropathic pain models and remain an important gap.

4.1 Evaluating the local and remote impact of PBMT on pain relief

Several studies have suggested that PBMT can produce effects beyond the immediate site of light application, potentially influencing tissues or wounds located at distant regions of the body (Gordon and Johnstone, 2019; Johnstone et al., 2021; Rochkind et al., 1989; Agrawal et al., 2014; Kim et al., 2017; Liebert et al., 2023). When PBMT is applied to body regions not directly related to the site of injury or is applied directly to circulating blood, as in intravascular laser irradiation of blood (ILIB), systemic physiological changes have been observed (Hagiwara et al., 2008; Tomé et al., 2020; Huang YY. et al., 2012; Silva and Pinheiro, 2021). These effects have been attributed to the modulation of immune and inflammatory responses, the activation of systemic vasodilation, or the release of endogenous analgesic substances, such as β-endorphins. Some studies suggest that PBMT targeting blood components may modulate mitochondrial function and oxidative stress, potentially contributing to therapeutic effects in tissues far from the irradiation site (Huang YY. et al., 2012).

However, whether these effects are mediated uniquely by blood-based mechanisms remains uncertain. Such effects, often referred to as "Remote PBMT" (Gordon and Johnstone, 2019; Johnstone et al., 2021; Kim et al., 2017), have been hypothesized to arise from changes in blood composition, including increases in immune cells and bone marrow-derived stem cells that home to sites of injury to enhance repair (Oron et al., 2022).

Other proposed mechanisms of PBMT include increased mitochondrial activity and ATP production, enhanced antioxidant defenses, modulation of inflammatory mediators, and endogenous opioid release (Hamblin, 2017; Huang YY. et al., 2012; Silva and Pinheiro, 2021; Agrawal et al., 2014; de Andrade et al., 2019). However, these outcomes have been demonstrated under varied experimental conditions, and not all have been consistently assessed in studies using local PBMT applications. For instance, De Andrade et al. (2017) reported reduced nociceptive behaviors in a peripheral nerve injury model (CCI) with local PBMT, but did not assess systemic biomarkers. In contrast, studies employing intravascular or remote PBMT have shown improvements in mitochondrial function and reductions in systemic oxidative stress and inflammation (Silva and Pinheiro, 2021; Huang SF. et al., 2012), indicating that some effects may be systemically mediated. Notably, Agrawal et al. (Agrawal et al., 2014) and Hamblin (Hamblin, 2017) reviewed evidence suggesting that PBMT can modulate immune and neurochemical responses beyond the irradiated tissue, potentially influencing central and peripheral pain processing.

In the context of peripheral nerve injury, this raises the possibility that remote PBMT may counteract elevations in circulating proinflammatory mediators (Grace et al., 2016; Grace et al., 2017; Grace et al., 2019), which contribute to the maintenance of NP. While blood-borne cytokines can indeed reach the site of injury, their systemic regulation through remote PBMT could offer an additional therapeutic avenue distinct from local anti-inflammatory or antioxidant mechanisms (Figure 1).

To facilitate comparison across the body of evidence, we provide below an integrated summary of the main preclinical and clinical studies investigating photobiomodulation in neuropathic pain models (Table 2).

5 Challenges and knowledge gaps

5.1 Lack of standardization in PBMT protocols

Personalized medicine involves developing treatment strategies tailored to the characteristics that make each patient unique (Goetz and Schork, 2018). Several challenges are associated with implementing personalized PBMT protocols, particularly due to the absence of practice guidelines that account for individual anatomical differences, skin pigmentation, and body mass index, as well as the difficulty in determining optimal parameters such as dose, frequency, intensity, application site, and duty cycle. We regard these as the main limitations in achieving truly personalized PBMT protocols.

Few studies exploring remote/systemic PBMT in NP: While PBMT has demonstrated neuroprotective effects on various cellular elements (Pogrel et al., 1997), little is known about the mechanisms underlying remote/systemic PBMT. The central challenge in this modality is how to evaluate the indirect effects of PBMT applied to distant, non-irradiated tissues or organs, such as the brain (Kim et al., 2017). A study conducted by Ganeshan et al. (2019) explored these limitations by using remote PBMT as a preconditioning treatment regimen, in which PBMT was administered concurrently with MPTP insult, a model of Parkinson's disease. In that study, daily preconditioning with remote PBMT for 10 days provided significant neuroprotection against MPTP insult (Ganeshan et al., 2019). However, few studies have investigated the optimal parameters for remote/systemic PBMT or identified which tissues or organs may encompass the greatest beneficial effects. Although the potential of PBMT as a treatment for many clinical conditions has long been studied and validated, further research on remote/systemic PBMT is required to determine the most effective application sites and optimal dosing.

5.2 Underreporting of sex-based differences in response

Sex-specific differences have been observed across a range of physiological and pathological conditions (Lovejoy et al., 2009; Tse et al., 2016; Regitz-Zagrosek and Kararigas, 2017). A few studies have been conducted to address the effects of gender differences in PBMT, and the analysis of these studies provides preliminary evidence that gender may be as important as skin color in determining individual responses to PBMT (Liebert et al., 2022). In line with the above, there is no doubt that including reports on sexual dimorphism is essential for improving the accuracy and reproducibility of tissue- and cell-based studies. Hormonal differences, body composition (e.g., fat distribution and muscle

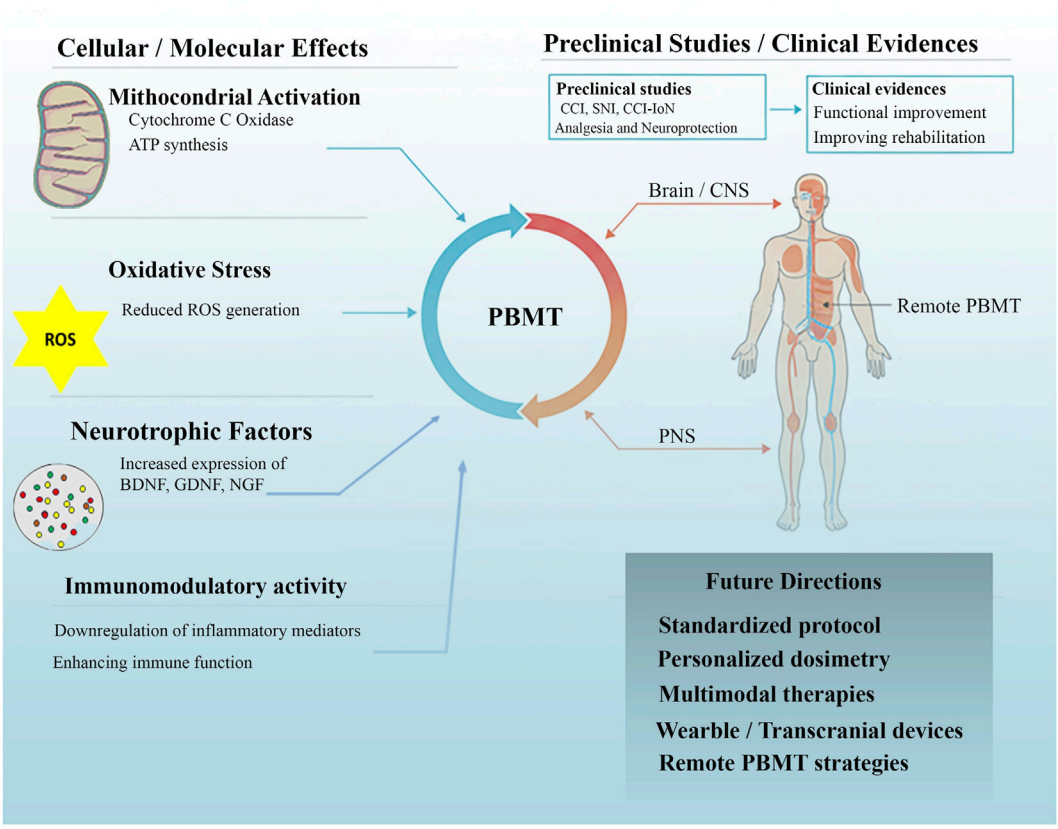

FIGURE 1
Presumed cellular and molecular mechanisms of PBMT, as inferred from animal and human studies where PBMT was delivered to the body and possible future directions for PBMT research. ATP, adenosine triphosphate; BDNF, brain-derived neurotrophic factor; CCI, chronic constriction injury; CCI-IoN, chronic constriction injury of infraorbital nerve; CNS, central nervous system; GDNF, glial-derived neurotrophic factor; NGF, nerve growth factor; Photobiomodulation therapy (PBMT); PNS, peripheral nervous system; ROS, reactive oxygen species; SNI, spared nerve injury.

TABLE 2 Comparative summary of preclinical and clinical evidence on PBMT for neuropathic pain. The table synthesizes experimental models, clinical conditions, PBMT parameters typically used, and the primary outcomes reported across studies.

Study type	Model/condition	PBMT parameters (range)	Main outcomes	Species/population
Preclinical	Chronic Constriction Injury (CCI)	660–830 nm; 1–10 J/cm^2; CW or pulsed	↓ Mechanical allodynia; ↓ Thermal hyperalgesia; ↓ IL-1β, TNF-α; ↑ IL-10; ↓ glial activation; ↑ axonal regeneration	Rats or mice; mostly males (limited female data)
Preclinical	Spared Nerve Injury (SNI)	808–980 nm; 4–8 J/cm^2	↓ Allodynia; ↓ microglial activation; improved nerve conduction	Rats; males
Preclinical	Diabetic neuropathy (STZ-induced)	660–904 nm; 3–10 J/cm^2	↓ Pain hypersensitivity; ↓ oxidative stress; ↑ mitochondrial function	Rats or mice
Preclinical	Infraorbital nerve injury/Crush models	660–808 nm	↓ Inflammatory markers; ↑ neurotrophic factors (BDNF); improved regeneration	Rodents
Clinical	Diabetic Peripheral Neuropathy	810–830 nm; 4–12 J/cm^2; multiple sessions	↓ Pain scores; ↑ nerve conduction velocity; improved QoL	Adults with diabetes
Clinical	Chemotherapy-induced peripheral neuropathy (CIPN)	635–850 nm; 4–10 J/cm^2	↓ Neuropathic pain; ↓ paresthesia; ↑ sensory recovery	Oncology patients
Clinical	Postsurgical neuropathic syndromes	808–904 nm; 4–8 J/cm^2	↓ Neuropathic pain; ↓ inflammation; faster recovery	Adults
Clinical	Entrapment/radiculopathy	830–980 nm	↓ Pain; improved nerve conduction; functional improvement	Adults

mass), and skin pigmentation can all influence light absorption and tissue responses to PBMT. A limited understanding of sex-specific responses may lead to suboptimal treatment outcomes for certain individuals, and failure to analyze data by sex could hinder researchers from uncovering valuable insights into the mechanisms of PBMT and its potential for targeted therapies.

6 Future perspectives

The preclinical evidence spans diverse injury paradigms, including nerve crush, ischemia–reperfusion injury, neuroinflammation, and peripheral musculoskeletal trauma. In each context, PBMT consistently reduces inflammatory markers, increases energy metabolites, and enhances functional outcomes. Preclinical models firmly establish PBMT's capacity to modulate mitochondrial function, inflammation, and oxidative stress while promoting repair and neurological recovery. The robust mechanistic insights, centered on cytochrome c oxidase activation, NO release, ATP enhancement, and cytokine regulation, validate PBMT as a powerful therapeutic tool. These foundational studies are essential for guiding subsequent translational research, informing dosage and delivery strategies, and tailoring interventions to specific injury modalities.

7 Conclusion

PBMT represents a promising non-pharmacological strategy for the management of NP, supported by converging mechanistic, preclinical, and emerging clinical evidence. By modulating mitochondrial activity, oxidative stress, inflammation, and neurotrophic signaling, PBMT promotes cellular homeostasis, neural repair, and analgesia. Consistent findings across animal models demonstrate its capacity to reduce mechanical and thermal hypersensitivity, downregulate pro-inflammatory cytokines, enhance antioxidant defenses, and upregulate neuroprotective mediators such as BDNF.

Despite this encouraging evidence, the field faces significant methodological and translational challenges. The lack of standardized protocols, the wide variability in wavelength, dose, and treatment frequency, and the underrepresentation of female subject's limit reproducibility and generalization of results. Furthermore, although local PBMT has been extensively explored, remote or systemic applications, where light is delivered to regions distant from the site of injury, remain understudied. These remote effects likely involve systemic mitochondrial signaling and immune modulation, representing an exciting frontier for investigation. Future studies must therefore prioritize mechanistic depth, sex-based analyses, and cross-tissue assessments to unravel local versus systemic contributions to PBMT's therapeutic effects. Advances in wearable, transcranial, and integrated multimodal systems may further enhance accessibility and precision.

When integrating the available evidence, local PBMT using near-infrared wavelengths (particularly 800–900 nm) with moderate energy densities emerges as the most consistently effective strategy for neuropathic pain. This approach provides reliable tissue penetration and robust modulation of mitochondrial and inflammatory pathways, with the strongest preclinical and early clinical support. In contrast, remote PBMT, although highly promising for its systemic immune and metabolic effects, remains exploratory and requires further mechanistic clarification. LEDs and lasers appear comparably effective when dose and intensity are adequately matched, but lasers may retain advantages for deeper targets due to superior collimation and irradiance. Multimodal strategies, such as combining PBMT with exercise, electrical stimulation, or neuromodulatory techniques, represent a compelling avenue for future research given potential synergistic effects on neuroinflammation and plasticity.

In summary, PBMT stands as a biologically grounded and safe approach capable of addressing the multifactorial nature of neuropathic pain. The current body of evidence positions local PBMT as the most promising and clinically actionable modality for neuropathic pain, while remote PBMT and multimodal combinations represent innovative future directions. The integration of mechanistic insights with rigorous translational research will be essential to establish optimized, personalized PBMT protocols and ultimately to transform its promise into consistent clinical benefit.

Author contributions

DM: Writing – original draft, Methodology, Investigation, Writing – review and editing, Formal Analysis. IR: Methodology, Formal Analysis, Writing – review and editing, Writing – original draft. LW: Conceptualization, Supervision, Methodology, Writing – review and editing, Validation, Investigation, Writing – original draft. MC: Writing – original draft, Project administration, Supervision, Methodology, Visualization, Funding acquisition, Writing – review and editing, Resources, Conceptualization.

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