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Photobiomodulation for immunomodulation and inflammation control: evidence from cellular, animal, and clinical research

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This review presents a comprehensive analysis of in vitro, in vivo, and clinical studies on the effects of photobiomodulation (PBM) on immunomodulation and mitigation of inflammation. PBM has been proven to be a non-invasive and effective treatment modality that plays a crucial role in modulating immune responses and reducing inflammation. In in vitro studies, PBM (primarily using wavelengths of 630-810 nm) demonstrated immunological effects by suppressing the expression of pro-inflammatory cytokines (tumor necrosis factor-alpha, interleukin [IL]-6, IL-1β) while promoting the expression of the anti-inflammatory cytokine IL-10. Furthermore, in vivo studies using various animal models confirmed that PBM reduces inflammation and facilitates tissue repair and regeneration. Clinical studies have shown promising outcomes, wherein PBM has been shown to reduce inflammation and enhance therapeutic efficacy in conditions such as oral diseases and arthritis. Overall, PBM is regarded as a highly promising therapeutic approach for the treatment of inflammatory diseases. However, further research is needed to optimize treatment parameters and assess long-term safety.

Key words: Photobiomodulation; Low-level laser therapy; Immunomodulation; Cytokines; Inflammation

INTRODUCTION

Photobiomodulation (PBM) has evolved considerably over the past few decades to become a non-invasive therapy that utilizes light at specific wavelengths to induce physiological changes in cells and tissues. PBM has gained significant attention for its potential to modulate immune responses, reduce inflammation, promote wound healing, and facilitate tissue regeneration [1-3]. While traditional anti-inflammatory treatments often have side effects with long-term use, PBM offers a promising alternative with minimal adverse effects, primarily employing near-infrared (NIR) and visible light to enhance mitochondrial activity and adenosine triphosphate (ATP) production, thereby aiding tissue recovery and inflammatory regulation [4,5].

The mechanism of PBM is closely linked to its interaction with cytochrome c oxidase (COX), a key enzyme in the mitochondrial electron transport chain (ETC) responsible for oxygen reduction and ATP synthesis. As illustrated in Fig. 1, PBM enhances electron transfer efficiency within COX, improving the reduction of oxygen to water and ultimately increasing ATP production. COX absorbs photons in the red to NIR spectrum (600-1,000 nm), which induces conformational changes in its copper (CuA and CuB) and heme (a and a3) centers, thereby promoting electron flow

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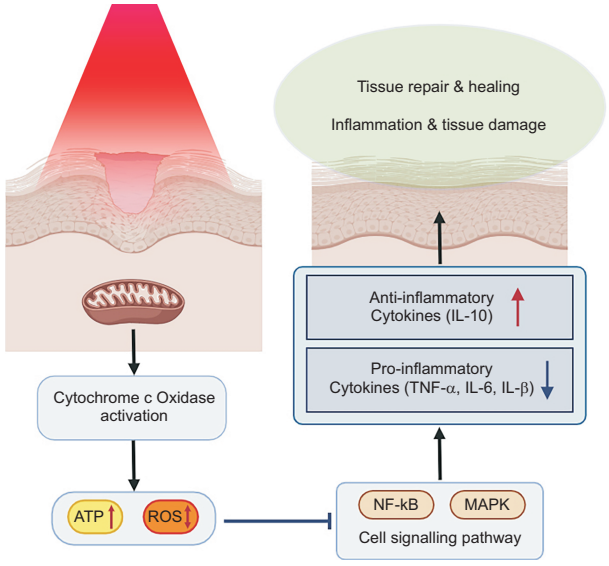

Fig. 1. Schematic representation of photobiomodulation's mechanism of action at the cellular level, showing primary photoreceptors, signaling pathways, and biological effects. IL, interleukin; TNF-α, tumor necrosis factor-alpha; ATP, adenosine triphosphate; ROS, reactive oxygen species; NF-κB, nuclear factor kappa B; MAPK, mitogen-activated protein kinase.

along the ETC [4,6]. This enhanced electron transport boosts oxidative phosphorylation, increasing cellular energy availability. Additionally, PBM influences reactive oxygen species (ROS) modulation, which is critical for cellular signaling and oxidative stress control. ROS are chemically reactive molecules that serve as signaling messengers in immune responses but can cause oxidative damage when overproduced. PBM helps maintain a balance between ROS generation and antioxidant enzyme activation, protecting cells from oxidative stress-induced damage [7,8].

Beyond its role in cellular energy metabolism, PBM significantly contributes to immune regulation and inflammation control. Chronic or excessive inflammation is often driven by pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-1β, which activate immune responses and exacerbate inflammatory conditions. PBM reduces immune activation by downregulating pro-inflammatory cytokines while upregulating IL-10 and transforming growth factor-beta (TGF-β), aiding tissue repair [9,10].

A critical pathway involved in PBM-induced immune modulation is nuclear factor kappa B (NF-κB) signaling, a major regulator of inflammation and immune responses. NF-κB is a transcription factor that controls the expression of pro-inflammatory cytokines and stress-response genes. When activated, it promotes inflammatory gene transcription, leading to sustained inflammation in chronic conditions [11]. PBM inhibits excessive NF-κB activation, helping to reduce prolonged inflammation and tissue damage. Another key pathway influenced by PBM is the mitogen-activated protein kinase (MAPK) pathway, which regulates cell proliferation, stress responses, and cytokine production. PBM modulates this pathway by reducing inflammation-driven MAPK activation, further contributing to its anti-inflammatory effects [12].

Persistent inflammation can lead to conditions such as rheumatoid arthritis, autoimmune diseases, and neuroinflammation [13-15]. By enhancing mitochondrial bioenergetics and regulating key inflammatory pathways, PBM presents a promising therapeutic strategy for inflammation control and cellular recovery (Fig. 1).

Despite increasing evidence supporting PBM's efficacy across different inflammatory conditions, further research is needed to synthesize findings from in vitro, in vivo, and clinical studies to establish optimal treatment parameters. Through these mechanisms, PBM has emerged as a non-invasive and safe alternative for managing inflammatory diseases [3,5,10]. This review aims to comprehensively analyze PBM's immunological mechanisms and anti-inflammatory effects based on in vitro, in vivo, and clinical research. Additionally, it seeks to identify optimized treatment conditions and highlight areas requiring further investigation, ultimately exploring the broader clinical applications of PBM.

METHODS

The author conducted a comprehensive literature search in the PubMed database to identify relevant articles published within the last 5 years using the keywords "PBM OR low-level laser therapy (LLLT) AND cytokines," which initially yielded 97 articles. To ensure relevance and methodological rigor, the screening process was performed based on title, abstract, and full-text review with clear inclusion and exclusion criteria. Articles were included if they investigated the effects of PBM or LLLT on cytokine modulation in various biological contexts, reported detailed PBM parameters (including wavelength, energy density, irradiation time, and treatment protocol) to ensure reproducibility, and were primary research articles presenting in vitro, in vivo, or clinical investigations. Conversely, systematic reviews, meta-analyses, case reports, conference abstracts, and studies lacking detailed PBM parameters were excluded, as were articles not directly addressing PBM's effects on cytokines.

Following this process, 30 articles were selected for review, comprising 12 in vitro studies that explored cellular-level cytokine modulation in controlled laboratory settings, 12 in vivo studies investigating PBM's immune and inflammatory effects in animal models, and 6 clinical studies evaluating its impact on cytokine modulation in human subjects.

IN VITRO STUDIES

Numerous in vitro studies have confirmed that PBM reduces pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) and increases anti-inflammatory cytokines (IL-10, TGF-β), supporting its role in mitigating inflammation [16-21]. PBM also modulates oxidative stress by upregulating Nrf2, a key antioxidant regulator [22], and promotes tissue repair through elevated levels of growth factors and chemokines such as BDNF, Eotaxin-3, Fractalkine, and GCP2 [23]. Additionally, alterations in the OPG/RANKL ratio suggest PBM's contribution to bone formation [24, 25].

Treatment efficacy varies with protocols, including wavelength, energy density, and irradiation time. Some wavelengths produce distinct cytokine responses, and multi-wavelength applications may cause counteractive effects [26]. Dose-dependent outcomes have been observed regarding treatment session number and irradiation duration [27] (Table 1).

PBM therapy has been increasingly studied for its role in regulating immune responses, particularly through its effects on inflammatory cytokines, cellular metabolism, and tissue repair mechanisms. The studies listed highlight a variety of models, wavelengths, and treatment protocols, each contributing unique insights into PBM's immunomodulatory effects [28,29]. However, several contextual factors and variabilities must be considered when interpreting these results.

The role of cell type and tissue specificity in PBM-induced immune modulation

A critical aspect of PBM research is the specificity of its effects across different cell types and tissues. The reviewed studies involve various human and murine cells, including fibroblasts, keratinocytes, macrophages, mesenchymal stem cells, microglia, and epithelial cells. Each of these cell types exhibits distinct signaling pathways, metabolic states, and baseline immune responses, which can lead to differential PBM outcomes.

Several studies (e.g., Rahbar Layegh et al. [23], Genah et al. [30]) have demonstrated PBM-induced fibroblast activation leading to increased secretion of growth factors and cytokines, promoting tissue repair. However, in inflammatory conditions, fibroblasts may contribute to pro-inflammatory signaling, as seen in conditions such as fibrosis or chronic wounds. Studies like Jahani-Sherafat et al. [17] and Woo et al. [27] indicate that PBM can shift macrophages toward an anti-inflammatory M2 phenotype, upregulating IL-10 and TGF-β while suppressing TNF-α and IL-6. This highlights the importance of PBM in regulating innate immune responses and modulating macrophage plasticity. PBM effects on keratinocytes (e.g., Sá et al. [26], Salman et al. [22]) demonstrate differential cytokine regulation depending on the stimulus. For instance, while some protocols reduced TNF-α and IL-6 expression, others upregulated IFN-ɣ and IL-10, suggesting that PBM's impact depends on the inflammatory state of the cells.

The mechanism by which PBM regulates cytokines varies depending on the cell type. Macrophages and keratinocytes respond differently to PBM due to their distinct physiological roles, signaling pathways, and immune response characteristics. Macrophages are key players in innate immunity, producing pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) upon pathogen infection or tissue damage. However, they can transition from an M1 (pro-inflammatory) to an M2 (anti-inflammatory) state, secreting IL-10 and TGF-β. In contrast, keratinocytes primarily function as a physical barrier against external stimuli and tend to continuously secrete pro-inflammatory cytokines (TNF-α, IL-6, IL-8) when stimulated. When PBM is applied to macrophages, activation of COX enhances ATP production, leading to increased ROS and nitric oxide (NO) production (Fig. 1). This activates the Nrf2 pathway, enhancing antioxidant responses, while inhibiting the NF-κB pathway, which suppresses pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) [31]. Simultaneously, IL-10 and TGF-β levels increase, promoting the transition from M1 to M2 macrophages. Thus, PBM in macrophages facilitates immunosuppressive and anti-inflammatory effects. However, in keratinocytes, PBM increases mitochondrial activity and ATP production, which activates the MAPK (p38, ERK) and NF-κB pathways, leading to increased secretion of TNF-α, IL-6, and IL-8. Additionally, PBM-induced ROS production may trigger a stress response in keratinocytes [32,33]. Consequently, PBM may exert an anti-inflammatory effect in macrophages but promote inflammatory responses in keratinocytes.

The study by Stepanov et al. [34] on β-amyloid-stimulated microglia suggests PBM's potential in neurodegen-

Table 1. In vitro studies

Reference	Title	Model	Therapy protocol	Inflammatory and immune response regulator
Aguida et al. [16]	Near-infrared light exposure triggers ROS to downregulate inflammatory cytokines induced by SARS-CoV-2 spike protein in human cell culture	Primary human alveolar type II cells (HAECs) and a humanmacrophage cell line (THP-1)	Source: Synlyte PulseIR custom LED lamp Wavelength: 730 nm Power density: 6 W/m^2 Irradiation time: 10 minutes/4 sessions (HAECs), 8 sessions (THP-1)	Upregulation: IL10, TGF-β Downregulation: IL6, IL8, IL1-β, TNF-α
Jahani-Sherafat et al. [17]	The effect of photobiomodulation and *Akkermansia muciniphila* on THP-1 derived macrophage polarization treated with gliadin peptide	Gliadin stimulated THP-1 derived macrophages	Source: aluminum-gallium-arsenide (AlGaAS) diode laser Wavelength: 810 nm Energy density: 1 J/cm^2 Irradiation time: 24 hours	Upregulation: TGF-β, IL-10 Downregulation: IL-6
Yamauchi et al. [18]	High-intensity red light-emitting diode irradiation suppresses the inflammatory response of human periodontal ligament stem cells by promoting intracellular ATP synthesis	TNF-α-induced PDLSCs	Source: LZ1-00R205 deep red LED Wavelength: 650 nm Power density: 400 mW/cm^2 Irradiation time: 15 seconds	Downregulation: IL-6, IL-8
Silva et al. [19]	Photobiomodulation mitigates Bothrops jararacussu venom-induced damage in myoblast cells by enhancing myogenic factors and reducing cytokine production	C2C12 myoblast cells	[660 nm] Source: aluminum gallium indium phosphide (InGaAlP) Power density: 400 mW/cm^2 Irradiation time: 10 seconds [780 nm] Source: gallium aluminum arsenide (Ga-AlAs) Power density: 500 mW/cm^2 Irradiation time: 10 seconds	Upregulation: IL-10 Downregulation: IL-6, IL-1β, TNF-α
Abidi et al. [20]	Immunomodulatory activity seen as a result of photobiomodulation therapy in stimulated primary human fibroblasts	Human periodontal ligament fibroblasts (hPDLFs)	Source: ultradent gemini laser Wavelength: 810 nm Power density: 0.625 W/cm^2 Irradiation time: 12.8 seconds	Downregulation: IL-6, IL17A/F, INF-ɣ, MCP-1, TNF-α
Guerra et al. [21]	Effect of photobiomodulation in an experimental in vitro model of asthma-Copd overlap	Human bronchial epithelial cells (BEAS-2B)	Source: diode laser (MM optics) Wavelength: 660 nm Energy density: 120 J/cm^2 Irradiation time: 180 seconds	Upregulation: IL-10, IFN-ɣ Downregulation: TNF-α, IL-1β, IL-6, IL4, IL-5, IL-13, IL-17, IL-21, IL-23
Salman et al. [22]	Photobiomodulation controls keratinocytes inflammatory response through Nrf2 and reduces langerhans cells activation	DNCB-treated human primary epidermal keratinocytes (HPEK)	Source: pulsed-wave LED Wavelength: 660 and 520 nm Power density: 12 mW/cm^2 Irradiation time: 250 seconds	Upregulation: Nrf2 Downregulation: TNF-α, IL-6, IL-8

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Table 1. Continued

Reference	Title	Model	Therapy protocol	Inflammatory and immune response regulator
Rahbar Layegh et al. [23]	Photobiomodulation therapy improves the growth factor and cytokine secretory profile in human type 2 diabetic fibroblasts	Type 2 diabetic human dermal fibroblasts (DHDFs)	Source: helium-neon laser Wavelength: 632.8 nm Power density: 2.618 mW/cm^2 Irradiation time: 192 seconds/2 sessions (24 hours, 72 hours)	Upregulation: BDNF, Eotaxin-3 (CCL26), Fractalkine (CX3CL1), GCP2 (CXCL6)
Hong et al. [24]	Effects of photobiomodulation on bone remodeling in an osteoblast-osteoclast co-culture system	Bone marrow-derived macrophages (BMMs) Primary pre-osteoblasts (calvarial osteoblasts, Cal-OBs)	Source: gallium-aluminum-arsenide (Ga-Al-As) laser Wavelength: 808 nm Power density: 1.2 J/cm^2 Irradiation time: single cell culture (5 days), co-culture (7 days)	[Co-culture] Upregulation: OPG Downregulation: RANKL
Monteiro et al. [25]	Photobiomodulation effects on fibroblasts and keratinocytes after ionizing radiation and bacterial stimulus	Human keratinocytes (HaCaT) Human gingival fibroblasts (HGFs)	Source: InGaAlP Wavelength: 660 nm Power density: 0.68 W/cm^2 Irradiation time: 2.8, 4.3, 5.7, 7.2 seconds	Increase: OPG Decrease: RANKL
Sá et al. [26]	Effect of photobiomodulation on inflammatory cytokines produced by HaCaT keratinocytes	Human keratinocytes (HaCaT)	Source: indium-gallium-aluminum phosphide semiconductor diode laser Wavelength: 660 and 808 nm Power density: 0.71 W/cm^2 Irradiation time: 7 seconds	[660 nm] Upregulation: IFN-α2 Downregulation: IFN-γ, IL-23 [808 nm] Upregulation: IFN-α2, IFN-γ, TNF-α, IL-6, IL-8, IL-12p70, IL-17A, IL-18, IL-23, IL-33, IL-10 [660 and 808 nm] Downregulation: IFN-α2, IFN-γ, IL-6, IL-8, IL-17A, IL-18, IL-23
Woo et al. [27]	Photobiomodulation enhances M2 macrophage polarization properties of tonsil-derived mesenchymal stem cells	Tonsil-derived mesechymal stem cells (TMSCs)	Source: LED array Wavelength: 630 nm Total energy: 0, 15, 30, and 60 J (15 J per one day) Irradiation time: 1,500 seconds	Upregulation: CCR2 (30 J), IL-1β (60 J), IL-1RA (30 and 60 J)

ROS, reactive oxygen species; LED, light emitting diode; IL, interleukin; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; ATP, adenosine triphosphate; PDLSC, periodontal ligament stem cell; IFN, interferon; MCP-1, monocyte chemoattractant protein-1; RANKL, receptor activator of nuclear factor kappa-B ligand; OPG, osteoprotegerin; Nrf2, nuclear factor erythroid 2-related factor 2.

erative conditions like Alzheimer's disease by reducing oxidative stress and inflammatory cytokines. This shows that PBM's effects extend beyond traditional inflammatory models to include neuroimmune interactions.

PBM's effects on immune modulation are highly dependent on the cell type and tissue microenvironment. Macrophages and epithelial cells may exhibit different cytokine responses compared to fibroblasts or neurons [3]. This suggests that PBM protocols should be tailored based on the target tissue and desired immunological outcome.

New mechanistic insights beyond initially established pathways

Early PBM research focused primarily on the reduction of oxidative stress, ATP production, and modulation of inflammatory cytokines [35,36]. However, emerging studies indicate additional mechanisms that extend beyond these foundational pathways.

PBM is known to modulate ROS levels, as observed in Aguida et al. [16], where NIR light triggered ROS-mediated downregulation of pro-inflammatory cytokines induced by the SARS-CoV-2 spike protein. This suggests that controlled ROS production may be a mechanism for PBM-induced immune modulation rather than merely reducing oxidative stress. Several studies (e.g., Brito et al. [37], Guerra et al. [21]) highlight PBM's role in inhibiting MAPK and NF-κB signaling, two key pathways in inflammatory cytokine production. Downregulation of NF-κB is associated with decreased IL-6 and TNF-α levels, which is consistent across multiple models, including bronchial epithelial cells and fibroblasts. Yamauchi et al. [18] demonstrated that PBM enhances intracellular ATP synthesis in periodontal ligament stem cells, reducing inflammation. This supports the idea that mitochondrial bioenergetics plays a crucial role in PBM-induced immune modulation. The study by Stepanov et al. [34] identified an upregulation of arginase in microglia, indicating a shift toward an anti-inflammatory phenotype. This suggests that PBM could influence amino acid metabolism and NO signaling, adding a new layer to our understanding of its neuroimmune effects.

As shown in Fig. 1, PBM's mechanisms extend beyond simple cytokine regulation, incorporating ROS signaling, mitochondrial bioenergetics, and NF-κB/MAPK pathway modulation. New insights into its role in neuroimmune function and metabolic pathways could expand its therapeutic applications.

Influence of pre-existing in vitro conditions on PBM outcomes

The initial cellular state and experimental conditions critically influence PBM efficacy, though they are often overlooked. Monteiro et al. [25] reported that PBM effects vary based on the presence of pre-existing inflammation, and Guerra et al. [21] found that PBM downregulated IL-6 and IL-1β in asthma-chronic obstructive pulmonary disease (COPD) models only after prolonged exposure, suggesting that pre-treatment conditions are crucial.

Co-culture studies further illustrate this complexity. Hong et al. [24] demonstrated that PBM reduced RANKL and increased OPG levels in osteoblast-osteoclast systems, indicating a role in bone remodeling. These findings highlight that intercellular interactions significantly affect PBM's immunomodulatory outcomes, requiring more sophisticated in vitro models.

PBM parameters also critically determine outcomes. Sá et al. [26] showed that 660 and 808 nm light produced distinct cytokine responses in keratinocytes, while Aguida et al. [16] found that repeated exposures were necessary to significantly elevate IL-10 and TGF-β levels, emphasizing the importance of wavelength, dosage, and treatment duration.

Overall, in vitro studies demonstrate PBM's ability to decrease pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) and increase anti-inflammatory cytokines (IL-10, TGF-β), while modulating oxidative stress, mitochondrial bioenergetics, and key signaling pathways such as Nrf2, ROS, and NF-κB/MAPK (Fig. 1). Effects vary by cell type and condition, extending beyond cytokine modulation to neuroimmune regulation, bone remodeling, and amino acid metabolism. Tailored PBM protocols are essential for optimizing therapeutic outcomes based on tissue specificity and disease context.

IN VIVO STUDIES

In vivo animal models have confirmed PBM's immunomodulatory effects, consistent with in vitro findings (Fig. 2). PBM consistently downregulates pro-inflammatory cytokines and enhances anti-inflammatory cytokines across various biological systems. For example, 808 nm laser treatment suppressed inflammatory mediators in spinal cord injury [38], while 940 nm laser combined with plant extracts reduced IL-1β, TNF-α, and IL-6 levels in knee osteoarthritis [39]. In dry eye models, multi-wavelength LED treatment decreased IL-1β, IL-6, and TNF-α [40], and in asthma and acute lung injury models, 660 nm irradiation increased IL-10 and reduced pro-inflammatory

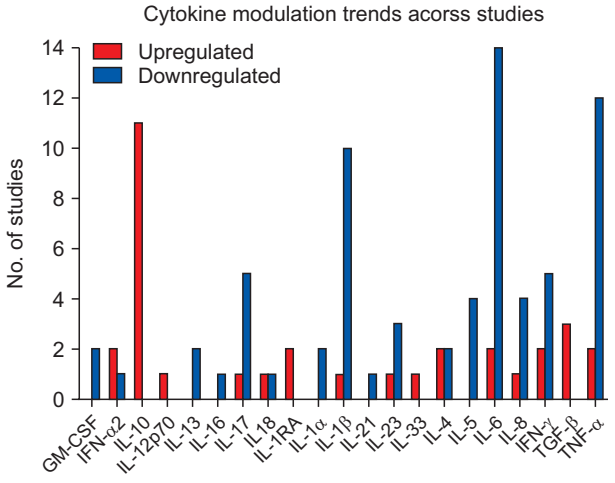

Fig. 2. A summary graph of the effects of photobiomodulation (PBM) on cytokine modulation based on both in vitro and in vivo studies. The red bars represent the number of studies reporting an increase in cytokine expression, while the blue bars indicate the number of studies reporting a decrease. PBM predominantly suppresses pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, while promoting the expression of anti-inflammatory cytokines such as IL-10 and TGF-β. This graph visually represents the overall immunomodulatory effects of PBM across different experimental models. TNF-α, tumor necrosis factor-alpha; IL, interleukin; TGF-β, transforming growth factor-beta; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon.

cytokines [41,42]. PBM has also shown benefits in models of oral ulcers, chronic wounds, rheumatoid arthritis, COPD, and chronic asthma by modulating IL-10, TGF-β, CREB, and MMP-2 expression [10,43-45] (Table 2).

While in vitro studies elucidate cellular mechanisms, in vivo models provide insights into systemic immune interactions and tissue-specific responses. However, challenges remain in translating cellular-level findings into whole-organism applications.

From in vitro to in vivo translation

In vitro studies serve as the foundation for understanding PBM's effects on specific immune and inflammatory pathways. However, in vivo studies are necessary to confirm whether these effects translate into functional immune modulation within a living system.

Many in vitro studies indicate that PBM can effectively downregulate pro-inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β) while upregulating anti-inflammatory cytokines (e.g., IL-10, TGF-β), suggesting its potential for immune modulation. This trend is confirmed in in vivo models such as those in de Brito et al. [10] (murine asthma model) and Alonso et al. [42] (asthma model in rats), where similar cytokine modulation patterns were observed, indicating PBM's ability to regulate immune responses in systemic diseases. However, factors such as blood circulation, immune cell migration, and tissue heterogeneity can either enhance or suppress PBM effects, leading to differences between in vitro and in vivo outcomes. Additionally, while in vitro studies such as Jahani-Sherafat et al. [17] and Woo et al. [27] demonstrated PBM-induced M2 macrophage polarization, in vivo studies like Ryu et al. [43] (oral ulcer model) and Shalaby et al. [46] (olfactory function recovery in mice) further confirmed that PBM increases IL-10 levels and reduces TNF-α, reinforcing its systemic impact on macrophage reprogramming. However, systemic immune responses involve complex interactions between multiple cell types and organs, which in vitro models cannot fully replicate. Moreover, PBM's effect on wound healing has been observed across different cell types such as fibroblasts, keratinocytes, and epithelial cells in vitro, with studies like Pavlov et al. [47] (chronic wound healing in rats) confirming these findings in vivo by demonstrating enhanced tissue repair.

Nevertheless, tissue perfusion, vascularization, and extracellular matrix composition significantly influence PBM's biological effects in living organisms compared to controlled cell cultures, highlighting the importance of adapting PBM protocols to specific physiological conditions [48].

Limiting factors of using PBM in vivo compared to in vitro

Despite its promising results, PBM therapy faces several limitations when applied in vivo.

In in vitro models, PBM is applied directly to cultured cells, ensuring uniform irradiation exposure. However, in vivo, light penetration is significantly influenced by tissue depth, pigmentation, and absorption properties, which can affect the actual dose received by target cells. For instance, deeper tissues such as muscles, joints, and nerves require NIR wavelengths (e.g., 808, 940 nm) for sufficient penetration, whereas superficial tissues like skin and mucosa respond more effectively to red light (e.g., 630, 660 nm). Additionally, in vitro studies are conducted under controlled conditions, whereas in vivo, the immune system continuously adapts to external stimuli, leading to variability in immune and inflammatory states. Factors such as hormonal fluctuations, microbiota composition, and metabolic status can unpredictably influence PBM outcomes, making results less consistent across different individuals. For example, in asthma models (de Brito et al. [10], Alonso et al. [42]), cytokine

Table 2. In vivo studies

Reference	Title	Model/disease	Therapy protocol	Inflammatory and immune response regulators
de Brito et al. [10]	Photobiomodulation therapy restores IL-10 secretion in a murine model of chronic asthma: relevance to the population of CD4+CD25+Foxp3+ cells in lung	Mouse (Balb/c)/chronic asthma	Source: diode laser Wavelength: 660 nm Power density: 0.741 W/cm^2 Irradiation time: 50 seconds Number of session: 15 Number of points: 3	Upregulation: IL-10 Downregulation: IL-4, IL-5, IL-13, IL-1β, TNF-α, LTB_4
Ju et al. [38]	Photobiomodulation promotes spinal cord injury repair by inhibiting macrophage polarization through lncRNA TUG1-miR-1192/TLR3 axis	Mouse (C57BL/6)/spinal cord injury	Source: MW-GX-808 Wavelength: 808 nm Power density: 50 mW/cm^2 Irradiation time: 50 minutes/day Number of sessions: 3	Downregulation: TUG1, TLR3, TNF-α, IL-1α, IL-1β, IL-6, CXCL2, NF-κB, iNOS
Yamada et al. [39]	Photobiomodulation and Sida tuberculata combination declines the inflammation's markers in knee-induced osteoarthritis	Wistar rat/knee osteoarthritis	Source: gallium-arsenide diode laser Wavelength: 940 nm Energy density: 9 J/cm^2/point Irradiation time: 27 seconds	Downregulation: IL-1β, TNF-α, IL-6, Nox
Goo et al. [40]	The anti-inflammatory effect of multi-wavelength light-emitting diode irradiation attenuates dry eye symptoms in a scopolamine-induced mouse model of dry eye	Mouse (C57BL/6)/dry eye	Source: multi-wavelength LED Wavelength: 680, 780, 830 nm Power density: 20 mW/cm^2 Irradiation time: 2 minutes	Downregulation: IL-1β, IL-6, TNF-α
da Silva et al. [41]	Effect of systemic photobiomodulation in the course of acute lung injury in rats	Wistar rat/acute lung injury	Source: Biolambda LEDsabr-blackbox mini Wavelength: 660 nm Power dinsity: 33.3 mW/cm^2 Irradiation time: 150 seconds Number of seesion: 2	Downregulation: IL-6, IL-17A, IL-1β
Alonso et al. [42]	Transcutaneous systemic photobiomodulation reduced lung inflammation in experimental model of asthma by altering the mast cell degranulation and interleukin 10 level	Wistar rat/asthma	Source: Biolambda LEDsabr-blackbox mini Wavelength: 660 nm Power dinsity: 33.3 mW/cm^2 Irradiation time: 150 seconds	Upregulation: IL-10
Ryu et al. [43]	Improved healing and macrophage polarization in oral ulcers treated with photobiomodulation (PBM)	Sprague-Dawley (SD) rat/ oral ulcers	Source: WELS01 Wavelength: 808 nm Energy density: 63.69 mW/cm^2 Irradiation time: 120, 240, 480 seconds Number of session: 5	Upregulation: IL-10 (60 J), MMP-2 (30, 60 J) Downregulation: IL-6 (30, 60 J)

Table 2. Continued

Reference	Title	Model/disease	Therapy protocol	Inflammatory and immune response regulators
Kim et al. [44]	Investigating the relevance of cyclic adenosine monophosphate response element-binding protein to the wound healing process: an in vivo study using photobiomodulation treatment	SD rat/acute wounds	Source: WELS01 laser Wavelength: 808 nm Power density: 63.69 mW/cm^2 Irradiation time: 240 seconds Total energy: 60 J Nuber of sessions: 5	Upregulation: TGF-β, CREB
de Brito et al. [45]	Effect of photobiomodulation in the balance between effector and regulatory T cells in an experimental model of COPD	Mouse (C57BL/6)/ chronic obstructive pulmonary disease (COPD)	Source: diode laser Wavelength: 660 nm Power density: 0.37 W/cm^2 Irradiation time: 180 seconds Number of session: 35	Upregulation: IL-10 Downregulation: IL-1β, TNF-α, IL-6, IFN-ɣ, MCP-1, GM-CSF, KC/CXCL1
Shalaby et al. [46]	Photobiomodulation therapy restores olfactory function impaired by photothrombosis in mouse olfactory bulb	Mouse (C57BL/6)/photothrombosis	Source: laser Wavelength: 808 nm Energy density: 325 mW/cm^2 Irradiation time: 2 minutes Number of session: 6	Upregulation: IL-1RA, IL-4, IL-10, sICAM-1 Downregulation: C5/C5a, IL-1α, IL-1β, IL-16, IL-17, IFN-ɣ, TNF-α
Pavlov et al. [47]	Features of cellular and molecular mechanisms of re-gulation of reparative processes in chronic wounds using photobiomodulation therapy	Wistar rat/chronic wounds	Source: lika-therapist M Wavelength: 660 nm Energy density: 1 J/cm^2 Irradiation time: 60 seconds Number of session: 5	Upregulation: IL-4 Downregulation: TNF-α
Cardoso et al. [49]	Improved spatial memory and neuroinflammatory profile changes in aged rats submitted to photobiomodulation therapy	Wistar rat/aging	Source: diode laser Wavelength: 810 nm Power density: 0.0357 mW/cm^2 Irradiation time: 30 seconds Number of point: 5 Number of session: 58 (consecutive days)	Upregulation: IL-6, IL-10, TNF-α Downregulation: IL-5, GM-CSF, MCP-1, LIX, IP-10, Fractalkine

IL, interleukin; TNF-α, tumor necrosis factor-alpha; LTB_4, leukotriene B_4; NK-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; LED, light emitting diode; TGF-β, transforming growth factor-beta; GM-CSF, granulocyte-macrophage colony-stimulating factor; KC/CXCL1, keratinocyte-derived chemokine/chemokine ligand 1; CXCL2, chemokine ligand 2; iNOS, inducible nitric oxide synthase; sICAM-1, soluble intercellular adhesion molecule-1; Nox, NADPH oxidase; MMP-2, matrix metalloproteinase-2; BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP response element-binding protein.

modulation was observed, but patient-specific immune differences could lead to variable responses in clinical applications. Another challenge is treatment dosage and consistency, as in vitro studies use precisely controlled irradiation times and intensities, whereas in vivo, factors like body size, tissue properties, and external environmental influences can alter the amount of light actually absorbed by the target area. This can make it difficult to standardize PBM treatments for clinical applications.

Ultimately, optimizing PBM for in vivo use requires careful consideration of light penetration, immune variability, and standardized treatment parameters to ensure reliable therapeutic effects.

The role of animal models in PBM treatment for immune modulation

The choice of animal model significantly affects PBM outcomes, as different species and disease models exhibit distinct immune responses.

Many PBM studies utilize induced disease models, where chemical or mechanical methods are used to replicate human diseases, such as asthma (de Brito et al. [10], Alonso et al [42].), osteoarthritis (Yamada et al. [39]), and wound healing (Pavlov et al. [47], Ryu et al. [43]). These models are valuable for studying acute and chronic inflammation, but they do not fully capture the complexity of naturally occurring diseases. In contrast, genetically modified models allow researchers to investigate PBM's effects on specific immune pathways by using genetically altered mice. For instance, Ju et al. [38] (spinal cord injury model) examined how the lncRNA TUG1-miR-1192/TLR3 axis contributes to PBM-induced immune modulation. While these models provide detailed mechanistic insights, they may not fully reflect the interactions of the human immune system. On the other hand, naturally occurring disease models, such as studies on aged rats (Cardoso et al. [49]), investigate spontaneous disease development and allow researchers to explore conditions like neuroinflammation and immune aging. Although these models offer greater clinical relevance, they are less controlled than induced models, making standardization more challenging.

Overall, each animal model has distinct strengths and limitations: induced models offer controlled conditions, genetic models enable precise mechanistic studies, and naturally occurring models provide better clinical applicability.

Differences in tissue response to PBM for immunomodulation

PBM effectively modulates inflammation in skin and mucosal tissues due to direct light exposure, benefiting conditions involving keratinocytes, Langerhans cells, and oral ulcers [22,43]. Red light (630-660 nm) is optimal for superficial tissues, while NIR light (808-940 nm) penetrates deeper to target bones and joints, influencing RANKL and OPG expression crucial for bone remodeling [24,39]. PBM also exhibits neuroprotective effects by modulating microglial activity and cytokine responses, as shown in Alzheimer's and olfactory recovery models [34,46]. Although neural applications require longer exposure due to the blood-brain barrier.

In vivo studies confirm PBM's ability to reduce pro-inflammatory cytokines (IL-1β, TNF-α, IL-6) and increase anti-inflammatory factors (IL-10, TGF-β) across diverse conditions, including spinal cord injury, osteoarthritis, asthma, chronic wounds, and neuroinflammation. PBM's effects vary depending on disease characteristics and tissue environment, with distinct cytokine responses in chronic versus acute inflammation models.

While in vitro studies elucidate mechanisms at the cellular level, in vivo research is essential to understand PBM's interactions with complex physiological systems like blood circulation and immune cell dynamics. However, limitations such as tissue penetration variability, individual immune differences, and treatment standardization challenges must be addressed. Optimal PBM parameters vary by tissue depth, with red light suited for superficial targets and NIR light for deeper structures. Animal models—induced, genetically modified, and naturally occurring—offer complementary insights but also present distinct advantages and limitations. Successful in vivo PBM application requires tailoring treatment protocols to tissue characteristics, immune responses, and precise irradiation settings (Table 2).

CLINICAL TRIAL STUDIES

Oral and mucosal conditions

Various clinical studies have evaluated the effects of PBM treatment on inflammation and immune responses. In oral conditions, Mutafchieva et al. [50] reported a reduction in the pro-inflammatory cytokine IL-1β following treatment with an 810 nm diode laser (1.2 J/cm^2) in patients with oral lichen planus. In contrast, Abboud et al. [51] found no significant changes in serum and salivary cytokine levels using a 660 nm GaAlAs diode laser (177 J/cm^2) for the same condition.

Martins et al. [52] conducted a randomized clinical trial on patients with radiation-induced oral mucositis and found that application of a 660 nm InGaAlP diode laser (6.2 J/cm^2) resulted in increases in TNF-α, IL-12p70, and IL-10, while levels of IL-1β and nitrite decreased.

Musculoskeletal and exercise-related studies

Regarding studies on muscle injury and inflammation, Tomazoni et al. [53] found that in elite soccer players, treatment with an 810 nm 5-diode cluster laser (2.75 W/cm^2, 100 seconds, at 17 points) led to increases in the antioxidant enzymes superoxide dismutase and catalase, along with reductions in the inflammatory cytokine IL-6 and the oxidative stress marker thiobarbituric acid reactive substances. However, Zagatto et al. [54] reported that the application of an 810 nm DMC laser (3.57 W/cm^2) in young water polo athletes did not result in significant changes in inflammatory markers.

In a study involving patients with knee osteoarthritis, Vassão et al. [55] demonstrated that PBM treatment using an 808 nm cluster laser (2 W/cm^2, 40 seconds, at 8 points, twice a week for 8 weeks) induced an increase in the anti-inflammatory cytokine IL-10 and a decrease in the pro-inflammatory cytokine IL-1β (Table 3).

Clinical trials on PBM have shown inconsistent results even for the same condition. In oral lichen planus, Mutafchieva et al. [50] reported a reduction in IL-1β with an 810 nm laser, while Abboud et al. [51] found no significant cytokine changes with a 660 nm laser. Similarly, Martins et al. [52] observed both pro- and anti-inflammatory cytokine changes in radiation-induced oral mucositis, but other studies reported unclear effects. In musculoskeletal conditions, Tomazoni et al. [53] found PBM reduced inflammation in soccer players, whereas Zagatto et al. [54] saw no significant changes in water polo athletes. Despite promising results, the variability in clinical outcomes underscores the need for a deeper exploration of study limitations and potential biases. One significant factor is the variation in PBM application protocols, including differences in wavelengths, energy densities, irradiation times, and session frequencies, making direct comparisons challenging. Additionally, many studies are limited by small sample sizes, which reduces statistical power and may contribute to inconsistent findings. Differences in patient populations, physiological responses, and disease severity further complicate the interpretation of results. Future research should aim to standardize PBM protocols and include larger, well-controlled trials to establish clearer clinical guidelines for its therapeutic applications.

FUTURE RESEARCH DIRECTIONS

Despite the promising potential of PBM therapy in immune modulation and inflammation control, several key areas require further investigation to enhance its clinical efficacy and widespread application. To ensure the most impactful advancements, research priorities should be established based on clinical urgency, feasibility, and potential for integration into medical practice.

Large-scale randomized controlled trials with longer follow-up periods (high priority)

While numerous in vitro and in vivo studies have demonstrated PBM's effectiveness, clinical trials remain limited in scale and duration, making it difficult to translate laboratory findings into real-world applications. To validate its therapeutic potential and facilitate regulatory approval, large-scale randomized controlled trials with diverse patient populations and extended follow-up periods should be prioritized. These trials should assess long-term efficacy, safety, and potential side effects, as well as compare PBM with conventional anti-inflammatory treatments. Generating robust clinical evidence will be crucial for integrating PBM into mainstream medical practice and gaining broader acceptance in clinical settings.

Standardization of PBM parameters for specific inflammatory conditions (high priority)

One of the most significant challenges in PBM research is the lack of standardized treatment parameters, such as wavelength, energy density, irradiation duration, and treatment frequency. Because different inflammatory conditions respond variably to PBM, determining disease- or tissue-specific optimal parameters is critical. To address this issue, we propose a standardized PBM protocol tailored to specific immune-related diseases, optimizing treatment parameters based on evidence from in vitro, in vivo, and clinical studies (Table 4). Future studies should focus on establishing evidence-based guidelines that ensure treatment consistency, reproducibility, and predictability, ultimately improving patient outcomes. Collaborative efforts among researchers, clinicians, and regulatory bodies are necessary to develop standardized protocols for clinical use.

Mechanistic studies exploring the interaction between PBM and specific immune cell populations (medium priority)

Although PBM has been shown to modulate inflammatory responses, its precise effects on different immune

Table 3. Clinical trials

Reference	Title	Disease	Therapy protocol	Inflammatory and immune response regulators
Mutafchieva et al. [50]	Histological improvement and cytokine levels reduction in patients with oral lichen planus after photobiomodulation therapy	Oral lichen planus (OLP)	Source: diode laser Wavelength: 810 nm Power density: 1.2 J/cm^2 Irradiation time: 30 seconds Sessions: three times a week for one month	Downregulation: IL-1β
Abboud et al. [51]	Serum and salivary cytokines in patients with oral lichen planus treated with photobiomodulation	OLP	Source: GaAlAs diode laser Wavelength: 660 nm Energy density: 177 J/cm^2 Irradiation time: 5 seconds Sessions: twice a week for 30 days	No significant modulation
Martins et al. [52]	The effect of photobiomodulation on nitrite and inflammatory activity in radiotherapy-induced oral mucositis: a randomized clinical trial	Oral mucositis	Source: InGaAlP diode laser Wavelength: 660 nm Energy density: 6.2 J/cm^2 Irradiation time: 10 seconds Numbers of points: 60+ Sessions: 5 (day 0, 7, 14, 21, 30)	Upregulation: TNF-α, IL-12p70, IL-10 Downregulation: IL-1β, Nitrite
Tomazoni et al. [53]	Infrared low-level laser therapy (photobiomodulation therapy) before intense progressive running test of high-level soccer players: effects on functional, muscle damage, inflammatory, and oxidative stress markers-a randomized controlled trial	Muscle damage and inflammation	Source: a five-diode cluster laser device Wavelength: 810 nm Power density: 2.75 W/cm^2 Irradiation time: 100 seconds Number of points: 17	Upregulation: SOD, CAT Downregulation: IL-6, TBARS
Zagatto et al. [54]	Effects of low-level laser therapy on performance, inflammatory markers, and muscle damage in young water polo athletes: a double-blind, randomized, placebo-controlled study	Muscle damage and inflammation	Source: DMC laser Wavelength: 810 nm Power density: 3.57 W/cm^2 Irradiation time: 30 seconds Number of points: 16 Sessions: 5 (everyday)	No significant modulation
Vassão et al. [55]	Effects of photobiomodulation and a physical exercise program on the expression of inflammatory and cartilage degradation biomarkers and functional capacity in women with knee osteoarthritis: a randomized blinded study	Knee osteoarthritis	Source: a cluster with 7 diodes Wavelength: 808 nm Power density: 2 W/cm^2 Irradiation time: 40 seconds Number of points: 8 Sessions: twice a week for 8 weeks	Upregulation: IL-10 Downregulation: IL-1β

IL, interleukin; TNF-α, tumor necrosis factor-alpha; SOD, superoxide dismutase; CAT, catalase; TBARS, thiobarbituric acid reactive substances.

cell populations remain insufficiently understood. Future research should focus on elucidating how PBM influences macrophages, T cells, B cells, and other key immune components involved in inflammation and autoimmunity. Advanced molecular and cellular studies will help clarify PBM's role in immune regulation, potentially leading to targeted therapeutic applications for specific inflammatory or autoimmune diseases. A deeper understanding of PBM's cellular mechanisms will also contribute to optimizing treatment protocols and improving clinical efficacy.

Development of personalized PBM protocols based on individual inflammatory profiles (medium priority)

Since inflammation varies significantly between individuals due to genetic, environmental, and lifestyle factors, a one-size-fits-all PBM approach may not be ideal [56,57]. Future research should focus on developing personalized PBM protocols that are tailored to an individual's inflammatory profile, disease stage, and immune status. This could be achieved through biomarker analysis, patient-specific treatment optimization, and integration of artificial intelligence or machine learning models to predict treatment responses. Personalized PBM strategies have the potential to enhance therapeutic efficacy and mini-

Table 4. Standardized photobiomodulation protocol for immune and inflammatory conditions

Category	Representative conditions	Wavelength (nm)	Power density (W/cm^2)	Energy density (J/cm^2)	Irradiation time (sec)	Treatment frequency	Key reference
Superficial tissue inflammation	Oral lichen planus, oral mucositis, skin inflammation, oral ulcers	630-660	0.5-1.2	6-10	10-30	3x per week, 4+ weeks	Salman et al. [22], Rahbar Layegh et al. [23], Mutafchieva et al. [50], Abboud et al. [51], Martins et al. [52]
Deep tissue inflammation	Knee osteoarthritis, muscle inflammation, post-exercise recovery	800-940	1.5-3	40-100	40-100	2-3x per week, 4-8 weeks	Silva et al. [19], Hong et al. [24], Yamada et al. [39], Tomazoni et al. [53], Zagatto et al. [54], Vassão et al. [55]
Systemic and immune inflammation	Chronic asthma, acute lung injury, spinal cord injury	660-808	0.5-1	50-150	50-150	3-5x per week, 2-4 weeks	de Brito et al. [10,45], Guerra et al. [21], Ju et al. [38], Alonso et al. [42], Pavlov et al. [47]

The standardized photobiomodulation (PBM) protocol was developed based on in vitro, in vivo, and clinical studies to optimize treatment efficacy for various inflammatory conditions. The key parameters—wavelength, power density, energy density, irradiation duration, and treatment frequency—were determined considering tissue penetration depth, biological response, and clinical feasibility. Wavelength selection was based on the depth of the target tissue, with 630-660 nm applied for superficial tissues such as the oral mucosa and skin, and 800-940 nm for deeper structures like muscles, joints, and nerves. Power density was adjusted to ensure adequate energy delivery without overheating, with 0.5-1.2 W/cm^2 for superficial conditions and 1.5-3 W/cm^2 for deep-seated inflammation. Irradiation duration was set to balance treatment effectiveness and safety, ranging from 10-30 seconds for superficial applications to 40-100 seconds for deeper tissues. Energy density was optimized to stimulate biological responses while avoiding tissue stress, typically 6-10 J/cm^2 for superficial tissues and 40-100 J/cm^2 for deep inflammation. Treatment frequency varied based on study findings, with higher frequencies applied in preclinical research and practical weekly schedules adopted for clinical applications. This protocol serves as a structured framework for PBM standardization, enhancing reproducibility and clinical translation.

mize variability in patient outcomes.

By addressing these critical research areas, future studies can help refine PBM therapy, improve its clinical applicability, and establish it as a reliable and effective modality for managing inflammatory diseases.

Investigation of combined approaches (lower priority but high potential impact)

PBM has demonstrated synergistic effects when combined with other therapeutic modalities, such as anti-inflammatory drugs, immunomodulators, and regenerative medicine therapies [58,59]. Future studies should explore how PBM enhances drug efficacy, reduces drug dependency, or minimizes side effects, particularly in chronic inflammatory and autoimmune diseases. While this research area holds great potential for integrative treatment strategies, its priority is relatively lower compared to establishing clinical validation and standardization, which are prerequisites for broader adoption.

By addressing these critical research areas in order of urgency and clinical impact, future studies can help refine PBM therapy, improve its clinical applicability, and establish it as a reliable and effective treatment modality for managing inflammatory diseases. Large-scale clinical trials and standardization efforts should be prioritized to ensure widespread clinical adoption, while mechanistic insights, personalized approaches, and combination therapies will further expand PBM's therapeutic potential in the long term.

CONCLUSION

PBM is a non-invasive therapy that modulates immunity, reduces inflammation, and regulates mitochondria and oxidative stress. In vitro and in vivo studies have demonstrated that PBM decreases pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) while increasing anti-inflammatory cytokines (IL-10, TGF-β), thereby promoting immune homeostasis and tissue regeneration. While PBM's immunomodulatory effects have been confirmed across various cell types and tissues, differences in cellular responses, initial inflammatory states, and treatment protocols suggest that optimizing therapeutic parameters is essential. In vivo studies have further validated PBM's anti-inflammatory effects in models of asthma, osteoarthritis, chronic wounds, and neuroinflammation; however, factors such as light penetration depth, systemic immune interactions, and tissue-specific responses must be considered for clinical applications. Clinical studies have reported that PBM improves inflam-

matory markers and promotes tissue healing in conditions such as oral mucositis, osteoarthritis, and muscle injuries, yet inconsistencies in outcomes due to variations in irradiation intensity, treatment duration, and individual patient differences highlight the need for standardized PBM protocols tailored to specific diseases. Thus, while PBM holds great potential for immune modulation and anti-inflammatory therapy, future research should focus on large-scale clinical trials, mechanistic investigations of PBM's systemic immunomodulatory effects, and the development of disease-specific personalized treatment strategies.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIALS

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