Journal of Lasers in Medical Sciences

J Lasers Med Sci 2026;17:e51084

Review Article

https://journals.sbmu.ac.ir/jlms

doi:10.34172/jlms.51084

Photobiomodulation Therapy in COVID-19 Management: A Comprehensive Review of Mechanisms and Clinical Outcomes

Mehdi koushki[1,2], Rozhina Ghajarbeigi[3], Mahdis Nazari[4], Nasrin Amiri-Dashatan[4*], Masoumeh Farahani[5*], Somayeh Jahani-Sherafat[6]

[1]Cancer Gene Therapy Research Center, Zanjan University of Medical Sciences, Zanjan, Iran
[2]Department of Clinical Biochemistry, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[3]School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran
[4]Zanjan Metabolic Diseases Research Center, Health and Metabolic Diseases Research Institute, Zanjan University of Medical Sciences, Zanjan, Iran
[5]Proteomics Research Center, System Biology Institute, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[6]Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

***Correspondence to**
Nasrin Amiri-Dashatan,
Email: nasrinamiri91@gmail.com and
Masoumeh Farahani,
Email: mfarahani2005@gmail.com

Received: December 6, 2025
Accepted: February 24, 2026
ePublished: November 2, 2026

Abstract

Introduction: Emerging evidence infers that photobiomodulation therapy (PBMT) has gained attraction as a promising adjunctive in the management of COVID-19 due to its anti-inflammatory, immunomodulatory, and tissue-repairing effects. Given the limitations of current pharmacological interventions including adverse side effects and the persistent challenge of managing severe hyperinflammation, there is a critical need to investigate novel therapeutic approaches like lasers. PBMT utilizes red or near-infrared light to alleviate pro-inflammatory cytokines, and raise immune responses, potentially mitigating complications such as cytokine storms and acute respiratory distress syndrome (ARDS).

Methods: The purpose of this review was to critically evaluate the therapeutic potential of PBMT in COVID-19 management by synthesizing current clinical and preclinical evidence and to explore current treatment methodologies and mechaniss.

Results: Running methodologies include external application of red or infrared light, intranasal or intravenous laser therapy, and combined techniques with standard treatments. The clinical and preclinical data available on the use of PBMT indicate a reduction in inflammatory markers, improvements in oxygenation, and enhanced recovery programs among patients with COVID-19, with satisfactory safety profiles and minimal adverse effects. Mechanistically, PBMT acts by modulating mitochondrial function, increasing ATP generation, and inducing nitric oxide release, which collectively provide cytoprotective effects, improved blood flow, and reduced inflammation.

Conclusion: PBMT demonstrates significant therapeutic potential for COVID-19 management by effectively modulating the immune system and mitigating the cytokine storm. Its mechanisms involve reducing pro-inflammatory cytokines, enhancing mitochondrial function, and improving tissue oxygenation, which collectively alleviate symptoms and prevent severe complications like ARDS. While current evidence supports PBMT as a safe adjunctive therapy with minimal side effects, large-scale randomized controlled trials are essential to establish standardized protocols and confirm its clinical efficacy. The non-invasive nature of this treatment and the potential for at-home use make it a noteworthy candidate for further research and clinical applications.

Keywords: COVID-19, Photobiomodulation therapy, PBMT, Laser therapy, Mechanisms

Introduction

The coronavirus disease 2019 (COVID-19 has emerged as one of the most significant public health challenges in the world.[1] Following the detection of the initial cases, the swift transmission of the virus resulted in a global crisis due to its rapid infectivity and complex pathology.[2] The virus mainly affects tissues expressing angiotensin-converting enzyme 2 (ACE2) receptors, particularly in the upper and lower respiratory tracts. This results in significant inflammatory responses, which are marked by cytokine storms, pulmonary edema, and dysfunction of various organs, presenting considerable challenges to traditional treatment methods.[3,4] The pathological features and emergence of variants with significant mutations have further complicated disease management and highlight the need for novel therapeutic strategies and rapid adaptations in treatment approaches.[5]

Please cite this article as follows: Koushki M, Ghajarbeigi R, Nazari M, Amiri-Dashatan N, Farahani M, Jahani S. Photobiomodulation therapy in COVID-19 management: a comprehensive review of mechanisms and clinical outcomes. J Lasers Med Sci 2026;17:e51084. doi:10.34172/jlms.51084

Since the onset of the pandemic, researchers worldwide have undertaken an unprecedented effort to identify and develop effective therapeutic targets and treatments against SARS-CoV-2.[6,7] These efforts have resulted in various treatments, from direct antivirals aimed at inhibiting viral replication to immunomodulators designed to regulate the heightened immune response detected in severe cases of COVID-19.[8] Photobiomodulation therapy (PBMT) is a promising non-invasive modality that uses red and near-infrared light to reduce inflammatory activity and promote tissue repair.[9] Regarding COVID-19, several in vivo studies have been conducted on the use of PBMT on various aspects of COVID-19 disease.[10,11] Mechanistically, PBMT mitigates COVID-19-associated hyperinflammation by suppressing pro-inflammatory cytokines such as IL-6 and TNF-α and promoting compensatory anti-inflammatory processes.[12] Additionally, PBMT has demonstrated positive outcomes in managing post-COVID complications.[13] Considering its immunomodulatory, antiviral, and regenerative features, PBMT suggests a multi-faceted therapeutic procedure with remarkable potential to enhance current COVID-19 treatment methodologies.[13,14] This review critically assesses PBMT as a therapeutic intervention for COVID-19 by synthesizing existing clinical and preclinical data.

Methodology

A systematic literature search was conducted across Scopus, Google Scholar, PubMed, Embase, and WoS databases for English-language articles published from January 2015 to December 2025. Keywords included combinations of ("COVID-19" OR "SARS-CoV-2" OR "ARDS") AND "Cytokine Storm" AND ("Photobiomodulation Therapy" OR "PBMT" OR "Low-level Laser Therapy" OR "LLLT"). Two independent investigators screened titles, abstracts, and full texts based on inclusion (PBMT effects on COVID-19) and exclusion criteria (duplicates, irrelevant, non-English, and outdated). Relevant data from eligible studies were then extracted by three authors (Figure 1).

Photobiomodulation therapy: Principles

PBMT (or Low-Level Laser Therapy) is a non-invasive, non-thermal treatment that uses light to stimulate mitochondrial ATP production, effectively reducing pain and inflammation with minimal side effects.[15,16] Given the need for effective adjunctive strategies against severe COVID-19 complications like ARDS, PBM is a promising candidate. By using red to near-infrared light to target mitochondrial cytochrome c oxidase, the therapy stimulates cellular respiration, increases ATP production, and modulates nitric oxide and reactive oxygen species to improve physiological outcomes.[15] These downstream products reprogram cellular responses by modulating the inflammatory cascade and promoting pro-repair pathways.[15] The simultaneous release of nitric oxide after PBM stimulation promotes vasodilation and improves microcirculatory perfusion, all of which are particularly relevant to COVID-19 pathophysiology, where microvascular deficits and hypoxemia are prominent.[17]

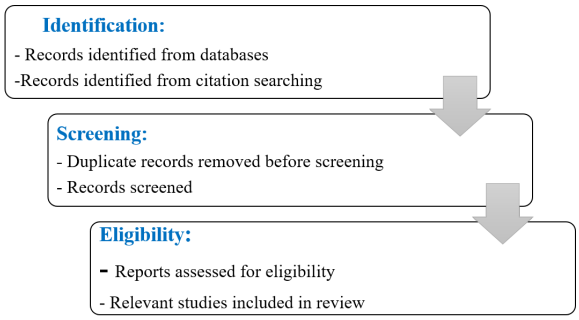


Figure 1. Flow Diagram of Study selection

PBM may provide a potentially effective therapeutic approach for COVID-19 by the following mechanisms: i) PBM enhances antiviral immune responses through increased levels of IFN-γ, which is an important activator of natural killer cells and lymphocytes, both of which have an essential role in COVID management,[17] ii) PBM enhances phagocytes' activation, improving their capacity to clear infectious pathogens,[17] iii) PBM promotes angiogenesis and increases tissue oxygenation, thereby improving pulmonary function and cellular metabolism, which, in turn, reduce tissue damage associated with hypoxemia,[17] and iv) PBM reduces cytokines such as IL-1β, IL-6, IL-8, and TNF-α, and suppresses the activity of COX-2, thus modulating the inflammatory response.[18] A number of therapeutic applications of PBM in COVID-19 have been proposed: i) Trans-thoracic PBM uses 810–970 nm wavelengths, which means deeper chest tissue penetration, thereby limiting pulmonary edema, improving gas exchange, and showing benefits in both preclinical and clinical settings,[17] ii) PBM suppresses profibrotic cytokines, modulates the inflammatory cascade in lung tissue, and improves lung capacity in patients with pulmonary fibrosis,[19] iii) Case studies have shown evidence of how PBM promotes healing in post-COVID orofacial manifestations both ulcerations and neuropathic pain among others,[20] iv) Baeder et al. reported significant recovery of herpetic-like oral lesions within 14 days following exposure to PBM [21] and a systematic review and meta-analysis by Pacheco et al. showed high levels of improvement in oral lesion healing with PBM alone, and even better results when applied in combination with photodynamic therapy (PDT),[22] v) The neuroregenerative effects of PBM have been reported, in addition to anti-inflammation on the olfactory mucosa,[13] vi) Oliveira et al. reported significant gains in scores on the University of Pennsylvania Smell Identification Test (UPSIT), a validated tool for assessing olfactory function, in post-COVID patients suffering from persistent olfactory loss receiving PBM therapy applied to each nostril in conjunction with a short course of prednisolone,[14] vii) Transcranial PBM promotes neurogenesis and synaptic plasticity and diminishes brain fog and cognitive disturbances, which have become recognized as post-COVID neurological sequelae,[23] and viii) Photobiomodulation can be given intravenously by inserting a fiber optic cable into the veins. When laser light is applied directly to blood cells flowing through the veins, it

speeds up the healing of ulcers and helps regulate the body's immune response.[17] The difference in biological effects is related to the different laser wavelengths to which tissues are exposed. Green light increases tissue oxygenation; blue light exerts antimicrobial activity and increases the production of nitric oxide, improving microvascular perfusion, while red light increases mitochondrial activity by enhancing the synthesis of ATP.

Current treatment methodologies (COVID-19)

The management of COVID-19 includes three combined strategies: vaccination, host-directed immunomodulators to suppress the inflammatory cascade, and antiviral agents that limit viral replication.[12] Therapeutic interventions have been broadly classified into four main categories [18]: 1) prevention of viral fusion and entry into host cells, 2) Inhibition of viral RNA replication within host cells, 3) enhancement of host immune responses, and 4) Modulation of cytokine storm and other excessive inflammatory reactions.

Antiviral agents play a central role in limiting viral replication. The intravenous antiviral medication remdesivir has been shown to have high effectiveness in shortening the recovery time of hospitalized patients.[24] Oral protease inhibitors, such as nirmatrelvir, are another crucial class of antiviral agents; these drugs decrease the risk of severe disease in high-risk outpatients and serve best when initiated within days of symptom onset in ambulatory settings.[25] Molnupiravir is another antiviral drug, which is mostly reserved for use in scenarios where first-line options are contraindicated or not available.[26] Dexamethasone, a corticosteroid taken systemically, has proven to significantly decrease mortality in patients requiring supplemental oxygen or mechanical ventilation.[27] Although their use is already established for the treatment of COVID-19 cases with moderate to severe symptoms, corticosteroids should be used cautiously because of their numerous adverse effects.[18] Furthermore, one systematic review and meta-analysis study in 2019 showed that corticosteroid therapy in post-influenza pneumonitis was associated with increased mortality, higher rates of superinfection, and higher risk of hospitalization.[28] Supportive interventions, including oxygen therapy, mechanical ventilation, and ECMO as a rescue modality in refractory hypoxemia, remain cornerstones of treatment.[29] Prone positioning further minimizes ventilator-associated lung injury in ARDS, a common and severe manifestation of COVID-19.[30] Because COVID-19 predisposes patients to thrombotic events, standard care should also include prophylactic anticoagulation.[31] Rehabilitation therapies, including physiotherapy, respiratory training, and cognitive rehabilitation, play an important role in improving respiratory function and mitigating neurological symptoms associated with the disease.[32] PBM is gaining global interest as an adjunctive therapy, notably through transthoracic irradiation. By utilizing near-infrared wavelengths (810–970 nm) delivered via the intercostal spaces, this method achieves deep lung penetration with minimal energy loss, offering a promising approach for treating pneumonia and influenza.[17,33,34]

Gene Expression Markers, Signaling Pathways, and Mechanistic Insights of PBMT in COVID-19

PBMT modulates a variety of gene-expression markers and signaling pathways that are crucial for mediating its biological effects in COVID-19. It has also been shown to downregulate several gene-expression markers associated with pro-inflammatory cytokines and pathways, while upregulating anti-inflammatory genes, particularly IL-10 mRNA.[35,36] Furthermore, a number of negative regulators of inflammation markers, antiviral gene markers, interferon-stimulated genes, and antioxidant-related genes are also upregulated by PBMT and can help balance the immune response.[37]

Inhibition of Pro-Inflammatory Cytokine Expression

In view of the known crucial roles played by TNF-α, IL-8, IFN-γ, IL-1β, and IL-6 in COVID-19- induced immune hyperactivation, a set of studies focused on the impact of PBMT on their gene expression. These studies have indicated that PBMT significantly decreases the mRNA and protein levels of inflammatory cytokines, and its effect is both fast-acting and durable, which counters its involvement in promoting cytokine storm and systemic inflammation.[38]

Modulating Different Transcription Factors

At the molecular level, the NF-κB signaling pathway can be listed as a leading anti-inflammatory mediator targeted by PBMT.[39] PBMT exerts potent anti-inflammatory effects by modulating key transcription factor pathways. It suppresses the NF-κB signaling cascade by inhibiting IKK-mediated phosphorylation of IκBα, thereby preventing the nuclear translocation of NF-κB dimers and the subsequent transcription of pro-inflammatory cytokines (e.g., IL-6, TNF-α).[40]

Additionally, PBMT modulates the JAK/STAT and AP-1 pathways; specifically, it attenuates AP-1-driven inflammation by regulating the MAPK cascade and reducing the phosphorylation of c-Fos and c-Jun.[41,42] Furthermore, while direct evidence is emerging, PBMT is hypothesized to enhance antiviral immunity by upregulating interferon-stimulated genes (ISGs), such as IFITM1 and IFITM3, which restrict viral entry and replication. These molecular modulations, supported by preclinical data, underscore PBMT's potential in mitigating hyperinflammation.[43,44] All mentioned molecular effects were supported by preclinical studies, some of which are addressed in Table 1.

Regulating Inflammasome Activation

Inflammasomes are multi-protein intracellular complexes that play an important role in innate immune responses by sensing pathogenic and host-derived stress signals. Upon activation, inflammasomes induce cleavage and activation of caspase-1, which processes pro-inflammatory

Table 1. Inflammatory gene/marker expression and associated treatment outcomes affected by PBMT in COVID-19

Targeted Gene/Marker	Expression direction affected by PBMT	Treatment outcomes	References
IL-6	Downregulates expression and protein secretion	Mitigates cytokine storm; reduces systemic inflammation	40,45
TNF-α	Decreases transcription and secretion	Limits tissue damage and inflammation	40
IL-1β	Inhibits inflammasome activation and caspase-1	Reduces pyroptosis and inflammatory amplification	46
IL-10	Upregulates anti-inflammatory cytokine	Promotes resolution of inflammation	47
IFN-γ	Modulates JAK/STAT pathway phosphorylation	Balances antiviral response and reduces immune-mediated tissue damage	48
CD177	Downregulates by reducing neutrophil ROS	Normalizes neutrophil activation and migration, attenuates excessive inflammation	49
TLR2	Downregulates receptor expression and signaling	Decreases MyD88-dependent NF-κB activation, reducing pro-inflammatory cytokines (TNF-α, IL-6, IL-1β)	50
NLRP3	Inflammasome Inhibits activation through mitochondrial stabilization and reduced ROS	Lowers caspase-1 activity, decreases IL-1β and IL-18 release, attenuates inflammatory cell death and cytokine storm	45
IL-8	Decreases chemokine expression	Reduces neutrophil recruitment and inflammation	45

cytokines such as IL-1β and IL-18 into their active forms, triggering strong inflammatory reactions.[51] The NLRP3 inflammasome is especially crucial in COVID-19 pathogenesis, as its hyperactivation leads to excessive inflammation and cytokine storm, resulting in severe lung tissue injury and systemic responses.[52]

Restoring Mitochondrial Function through Reducing Oxidative Stress-Related Genes, and Modulation of Calcium Signaling

Mitochondrial damage in COVID-19 triggers the NLRP3 inflammasome, leading to a pro-inflammatory cascade involving caspase-1 activation and the release of IL-1β and IL-18, which exacerbates tissue injury.[53] PBMT helps counter mitochondrial dysfunction by activating cytochrome c oxidase (CCO), which improves electron transport, reverses nitric oxide-related inhibition, and increases ATP production. By stabilizing mitochondria and limiting DAMP release, it may also reduce inflammasome activation, inflammatory cytokines, and pyroptotic cell death.[54,55] Accordingly, PBMT indirectly inhibits the priming and activation process of the inflammasome complex and suppresses the production of inflammatory cytokines and pyroptotic cell death.

PBMT exerts biphasic, context-dependent effects on reactive oxygen species (ROS). While shorter wavelengths (e.g., 660 nm) induce a transient, physiological rise in ROS that acts as a signaling mechanism to activate protective pathways via NF-κB and AP-1, longer wavelengths (e.g., 800 nm) and multi-wavelength protocols effectively reduce ROS levels. This modulation restores redox equilibrium and promotes an antioxidant response, highlighting the therapeutic versatility of PBMT in managing cellular oxidative states.[56,57] Such findings reinforce the potential role of wavelength choice in PBMT to achieve its antioxidant and anti-inflammatory properties.

PBMT regulates calcium signaling by stimulating light-sensitive ion channels (such as TRP channels). By utilizing blue (420 nm) and green (540 nm) wavelengths, this approach fosters controlled calcium influx, effectively restoring homeostasis and preventing the excessive levels that trigger inflammasome activation.[58] Additionally, PBMT regulates and maintains mitochondrial membrane potential, and calcium buffering prevents mitochondrial depolarization and the subsequent escape of inflammatory mitochondrial DAMPS.[54]

Modulating Caspase-1 Activity

PBMT inhibits the inflammatory cascade by suppressing caspase-1 activation, thereby preventing the maturation and release of IL-1β and IL-18. Mechanistically, by restoring mitochondrial integrity and mitigating oxidative stress, PBMT reduces the efflux of damage-associated molecular patterns (DAMPs). This normalization of mitochondrial function disrupts the feed-forward cycle of inflammasome assembly, effectively attenuating both local tissue damage and systemic inflammation.[46]

Upregulating Expression of Anti-Inflammatory Cytokine

The influence of PBMT on the expression levels of cytokines, and mainly the upregulation of anti-inflammatory cytokine IL-10, is indicative of its anti-inflammatory potential. PBMT induces all these through the previously mentioned sequence of events of mitochondrial cytochrome c oxidase activation, calcium ion channels opening, transient ROS generation, and NO release.[47] These are secondary messengers leading to redox-sensitive transcription factors such as NF-κB and AP-1, controlling gene expression downstream, including anti-inflammatory cytokines, cellular proliferation, and survival pathways.[59]

Modulating Immune Cell Activation Markers

PBMT modulates immune activation markers such as CD177 through linked mitochondrial and cellular signaling mechanisms. CD177 is a GPI-anchored protein, mainly expressed on a subset of human neutrophils and upregulated during intense neutrophil activation. It is downregulated by PBMT through decreased oxidative stress and alteration of the ROS production from neutrophils, leading to the recovery of the normal state concerning its activation and migration.[49]

PBMT also impacts Toll-like receptor 2 (TLR2) that is mainly expressed on immune cells by modulating its expression and activation, so there is a reduced recruitment of the MyD88 adaptor protein and a consequent inhibition of the NF-κB pathway with its downstream suppression of

proinflammatory cytokines.[60] In addition, PBMT induces autophagy via TLR2 modulation and thereby assists in regulating inflammation and improving tissue repair, as shown in spinal cord injury and neuroinflammation models.[50,61]

Study types: in vitro, in vivo, and clinical trials (COVID-19)

Given that PBM has shown promising effects in managing inflammation across many medical situations, such as COVID-19, it seems to be an alternative strategy to address the need for immune regulation in patients with moderate to severe COVID-19 disease. Numerous studies have been conducted in this field, and we intend to highlight the most recent research on the use of PBM for the treatment of COVID-19 in detail by type of study, including in vitro, in vivo, and clinical trials.

In vitro studies

In vitro studies have provided essential insights into the mechanisms by which PBMT may exert therapeutic benefits against COVID-19. Regarding the impact on virus replication, Zupin et al. found that the reduction in the viral load occurred when previously infected cells were exposed to all three tested wavelengths (450, 454, and 470 nm), with significant effects particularly observed at 48 hours post-infection.[62] Zupin et al. in another study applied a class IV laser medical device in a cellular model of SARS-CoV-2 infection, utilizing both blue and near-infrared wavelengths. They found that photobiomodulation therapy (PBMT) at blue wavelengths effectively inhibited viral replication when the virus was directly irradiated before being introduced to cell cultures, as well as when already infected cells were treated. Near-infrared (NIR) wavelengths were less effective, showing only a minor reduction in the viral load. Cells exposed to either the irradiated virus or directly irradiated themselves maintained viability similar to untreated cells. Their findings suggest that PBMT could be a viable in vitro strategy to counteract SARS-CoV-2 infection.[63] According to the previous reports, the ability of SARSCoV-2 to replicate in in vitro cellular models of infection can be efficiently affected by both blue and visible light, as reported. Given this evidence, a study examined the effects of blue light at 450, 454 and 470 nm on SARS-CoV-2 to evaluate the residual viral infectious potential on Vero E6, Caco-2 and Calu-3 cells, following the irradiation of viral particles.[64] The results indicated a strong block of viral amplification after 12 minutes of irradiation at 40 mW/cm2. Indeed, the viral load remained constant at 7 days post-irradiation/infection, just as it did one day post-irradiation/infection, and cellular viability was maintained at levels similar to those of control cells without infection.[64] Razzaghi et al. investigated the role of a low-power blue laser with a wavelength of 405 Nm in increasing the level of nitric oxide in increasing the resistance of cells to the COVID-19 virus. They found that LED light exhibits an antiviral effect.[65]

In vivo studies

It has been confirmed that PBMT alleviates inflammation in experimental models,[66,67] as well as in mice with chronic obstructive pulmonary disease (COPD).[68] An in vivo study by Macedo et al. demonstrated that PBMT could reduce inflammatory infiltrates, lung injury score, and immunoexpression of IL-1β in an acute lung injury experimental model in rats.[69] They reported that treatment with PBMT may help induce an adequate tissue response, capable of modulating the signs of the inflammatory process in acute lung injury (ALI).[69] Another study has used a zebrafish model to investigate the effects of PBM therapy on the cytokine storm syndrome (CSS) caused by COVID-19. The results showed that the PBM treatment significantly reduced oxidative stress markers in tissues, promoting an anti-inflammatory effect.[38] Consistent with broader clinical experience in respiratory care, the study by Sigman et al. reinforces the potential of PBMT as a feasible adjuvant strategy for COVID-19 patients.[70] Eilliams et al. suggested that whole-organ dynamic PBM is positively recommended for alleviating the symptoms of COVID-19.[71] The in vitro and in vivo studies on PBMT effects on COVID-19 infection are listed in Table 2. In this regard, some systematic reviews and meta-analyses revealed that PBMT has beneficial anti-inflammatory effects [36] and improves the outcomes related to COVID-19.[72]

Clinical trials

In this regard, Ehsani et al. evaluated the effects of PBMT on the respiratory function and laboratory parameters in COVID-19 patients with respiratory complications using a randomized, double-blind controlled design.[73] They revealed significant differences in CRP, IL-6, and O2 saturation between the photobiomodulation group and the control group after the completion of the five-session intervention.[73] In another clinical trial, Fatemi et al. reported that the use of intravenous laser irradiation improved oxygenation and reduced inflammatory markers, while also emphasizing the need for further studies to confirm these findings.[74] A preliminary clinical trial performed by Vetrici et al. also demonstrated that PBMT leads to improvement in pulmonary parameters like SMART-COP, BCRSS, RALE, and CAP (Community-Acquired Pneumonia questionnaire).[75] The results of a randomized, double-blind, placebo-controlled pilot trial indicated that PBMT in COVID-19 patients increases PO2 in the laser group compared to the control group, despite the higher levels of the CRP marker in the laser group than the control group, showing a positive correlation with the intervention time.[76] A placebo-controlled study involving 30 patients with severe COVID-19 conducted by Marchi et al. revealed that although the duration of ICU stay remained unchanged between the groups, those receiving 905/633/850 nm PBMT-sMF (PBMT in conjunction with a static magnetic field) exhibited a decrease in diaphragm atrophy, along with enhancements in ventilatory parameters and lymphocyte counts.[77] To determine the effectiveness of at-home self-administered PBMT for patients with COVID-19, Lim et al.

Table 2. Studies (including in vitro, in vivo, and meta-analysis) on PBMT Effects on COVID-19 infection

Study / country	Samples	Intervention	Outcomes
In vitro studies			
Zupin et al.[62], (2021)/Italy	In vitro model of SARS-CoV-2 infection (Vero E6 epithelial normal cell line)	LED photobiomodulation therapy (PBMT) at blue wavelengths (450, 454 and 470 nm)	• Reduction of viral load when previously infected cells were irradiated with all three wavelengths tested • Relevant effects noted 48 hours after infection (possibly disruption of the intracellular viral replication machinery by blue light)
Zupin et al.[64], (2022)/Italy	Vero E6, Caco-2 and Calu-3 cells infection model	Blue light at 450, 454 and 470 nm	• Block of viral amplification after the irradiation of viral particles. Following 12' of irradiation at 40 mW/cm2
Zupin et al.[63], (2023)/Italy	Vero E6 cells SARS-CoV-2 infection model	Blue and near-infrared (NIR) laser light	• Less efficacious of NIR wavelength and a minor effect on the reduction of the viral load • Preservation of virion integrity and antigenicity after blue and NIR irradiation (suggesting no correlation between PBMT antiviral effect with viral lipidic envelope disruption)
In vivo studies			
Sigman et al.[70], (2020)/USA	A 57-year-old African American man	Laser scanner with pulsed 808 nm and super-pulsed 905 nm modes for 28 min/ 4 once-daily PBMT sessions	• SpO2 increased from 93–94% to 97–100% • Oxygen requirement decreased from 2–4 L/min to 1 L/min • The RALE score improved from 8 to 5 • The Pneumonia Severity Index improved from Class V (142) to Class II (67) • Additional pulmonary indices (Brescia-COVID and SMART-COP) both decreased from 4 to 0. CRP normalized from 15.1 to 1.23
Macedo et al.[69], (2022)/Brazil	Twenty-four Wistar rats (*Rattus norvegicus*), weighing ± 272 g, 6 weeks old, were randomly divided into 3 groups (n = 8 per group) 1) Control group: animals without any intervention 2) Control ALI: acute lung injury in animals without treatment 3) ALI and PBM (ALIP): acute lung injured animals treated with PBM	Laser equipment (808 nm; 30 mw; 1.68 J) applied at three sites (anterior region of the trachea and in the ventral regions of the thorax, bilaterally) in the period of 1 and 24 h after induction of ALI	• reduced inflammatory infiltrates, thickening of the alveolar septum, and lung injury score • lower immunoexpression of IL-1β
Williams et al.[71], (2022)/USA	50-person case study of COVID-19-positive patients	A regimen of whole-organ deep-tissue transdermal dynamic PBM	• Significant reductions in the duration and severity of disease symptoms • Acute conditions were eliminated in 41/50 patients within 4 days of commencing PBM treatments • 50/50 patients fully recovering within 3 weeks with no supplemental oxygen requirements • SpO2 concentrations improved across the entire study population
Rosa et al.[38], (2023)/Brazil	Zebrafish model	Red PBM is an attractive therapy to downregulate the cytokine storm	• PBM treatment decreased the mRNA levels of pro-inflammatory and oxidative stress markers compared with rSpike in various tissues
Meta-analysis studies			
Study/country	**Included studies**	**Aim**	**Outcomes**
Raji et al.[72], (2021)/Iran	Preclinical and Clinical COVID-19 studies (animal models and clinical studies)	Evaluation of Protective Effect of PBM on the Inflammation of the Airway and Lung in COVID-19	• PBM therapy has beneficial anti-inflammatory effect, modulation of the immune system, lung permeability, or bronchoalveolar lavage on lung damage in both animal models and clinical studies
Pacheco et al.[22], (2022)/Brazil	5 articles with 11 clinical case reports	Assessment of the clinical evidence on the use of PBMT and aPDT for the treatment of oral lesions in patients infected with Sars-Cov-2	• PBMT and aPDT could be effective in the treatment of oral lesions of patients infected with Sars-Cov-2
Arjmand et al.[36], (2023)/Iran	Preclinical and Clinical COVID-19 studies (animal models and clinical studies)	Evaluation of probable effect of PBMT on the cytokine's mRNA expression in the lung in COVID-19	• This study demonstrated that PBMT is a potential treatment to decrease inflammatory conditions and lung damage in animal models and clinical studies in the COVID-19 field

PBM: Photobiomodulation; NIR: Near-infrared; LED: Light emitting diode; SpO2: Oxygen saturation; aPDT: antimicrobial photodynamic therapy

performed a randomized controlled trial from September 2020 to August 2021.[78] Patients were randomized to 1) the Control group receiving standard-of-care (SOC) only and 2) the Treatment group receiving SOC plus PBMT. The device was utilized for 20 minutes twice a day for a duration of 5 days, and thereafter, it was used once daily for 30 days. The researchers observed that patients with ≤ 7 days of COVID-19 symptoms recovered significantly quicker with PBMT compared to SOC. However, after 7 days, PBMT did not demonstrate any advantage over SOC.[78] Marashian et al. also carried out a randomized, double-blind, placebo-controlled pilot study examining the impact of PBM on serum cytokine responses in individuals with mild to moderate COVID-19.[45] They found that in the PBM group, there was a significant decrease in serum levels of IL-6, IL-8, and TNF-α compared to placebo.[45]

Clinical trials in Long & post-COVID-19

The condition following COVID-19, commonly referred to as 'long COVID', presents a significant clinical and scientific challenge for society. In this context, individuals who have recovered from COVID-19 exhibit a wide array of sequelae, which include muscular and articular lesions, as well as neurological, dermatological, and pulmonary complications. Consequently, rehabilitation therapies that utilize photobiomodulation, along with combined therapies, emerge as effective solutions to address these issues.[79] In this field, a single-blind, randomized controlled trial evaluated the local and systemic PBM in the treatment of dysgeusia in patients with long COVID. The findings showed that dysgeusia improved in both groups and proved that PBMT could be applied as a suitable option for dysgeusia treatment in long-COVID patients.[80] Soares et al. conducted a double-blind randomized clinical trial related to PBM, transmucosal laser irradiation of blood (TLIB), or B complex as alternatives to treat COVID-19-related long-term taste impairment.[81] The authors concluded that PBM, TLIB, and B complex could serve as potential treatment options for managing CRLTTI, despite the lack of total remission of taste and smell perception was not achieved after 8 sessions of PBM and TLIB or 30 days of B complex supplementation.[81] Elbanna et al. assessed the impact of PBM on post-COVID-19 functional capacity and fatigability in the elderly.[82] The authors found that after four weeks of PBM, the FSS level was suppressed substantially, and the KATZ score was significantly elevated.[82] These results indicate that the application of low-level laser PBM therapy in older adults post-COVID-19 could enhance functional performance, activities of daily living, and perception of fatigue, thereby affecting various physical, psychological, and mental aspects. Research indicates that xerostomia is present in cases of long COVID and can persist over time. The PBM has been extensively and effectively utilized in the management of xerostomia caused by various other factors. Recently, Oliveira et al. conducted a clinical trial to investigate the effects of a PBM protocol on long COVID xerostomia, oral functionality, and quality of life.[83] It is concluded that the PBM irradiation of the salivary glands could be studied as a future strategy to improve salivary production in patients with xerostomia due to long COVID.

Pulmonary fibrosis (PF) is a common long-term complication observed in post-COVID-19 patients, as it diminishes lung capacity, activates pro-fibrotic cells, and results in lung scarring. In this regard, Pereira et al. found that PBM in association with cardiopulmonary rehabilitation after COVID-19 could be extremely relevant for the recovery of pulmonary function in patients affected by PF.[19] Silva et al. in 2024 designed a study with the aim of investigating the efficacy of PBM association with physiotherapeutic rehabilitation in patients with post-COVID-19 PF.[84] The results indicated that the PBM1 group experienced a significant improvement in cardiopulmonary recovery compared to the PBM2 and Sham groups. Additionally, a comparison between the PBM2 and Sham groups revealed no significan difference.[84] From the results obtained, it can be concluded that the PBM using near-infrared radiation, associated with physiotherapeutic methods, demonstrated remarkable findings in the recovery of pulmonary function in patients with PF.

In a pragmatic randomized clinical trial, Campos et al. showed the effect of vascular photobiomodulation (VPBM) on the reduction of pain level in COVID-19 patients with tension-type headache (TTH).[85] Long COVID manifests as enduring neurological symptoms, such as brain fog, and offers few therapeutic alternatives. Intravenous laser irradiation of blood (ILIB) has been suggested as a possible treatment in a research study. Chang et al. investigated the effectiveness of ILIB in reducing symptoms of brain fog and analyzed the molecular mechanisms involved.[86] The results showed a significant improvement following ILIB treatment, indicating better cognitive function and enhanced sleep quality.[86] All of the clinical reports are listed in Table 3.

Current challenges and opportunities

While COVID-19 management relies on a mix of pharmacological and adjunctive therapies like PBMT, efficacy and safety limitations necessitate further research to optimize patient outcomes. Systemic corticosteroids demand cautious use, as they pose risks for hyperglycemia, osteoporosis, ulceration, and secondary infections.[16] Managing COVID-19 is complicated by potential drug interactions, specifically between systemic corticosteroids and protease inhibitors like nirmatrelvir and the disease's multi-organ nature, which necessitates a multidisciplinary treatment approach rather than relying solely on individual antivirals.[16] The constant viral mutations and newly emerging variants have further compromised the effectiveness of current therapeutic and preventive measures.[15] Global disparities limit access to advanced treatments, while PBMT offers a promising adjunctive option with a strong safety profile and low long-term risk.[87] Additionally, PBMT presents a reduced likelihood of bacteremia. Nevertheless, several challenges and limitations remain in its clinical application. Despite being a non-invasive and generally safe technique, PBMT has certain contraindications. One major restriction is its prohibition in cancerous lesions or benign lesions with malignant potential.[87] There are also conflicting views regarding its use during pregnancy. While some experts consider PBMT contraindicated throughout pregnancy, others limit this restriction to the first trimester.[87] Further challenges include the small sample sizes of existing clinical trials on PBMT's efficacy and contraindications. In patients with a history of seizures, PBMT may increase the risk of seizure recurrence and abnormal neurological activity.[87] Caution is also warranted when PBMT is applied over the gonads or the epiphyseal plates of children.[87] Several adverse effects have been reported, including ocular complications, which necessitate proper protective measures for both clinicians and patients, fatigue due to hormonal alterations, and hypotensive episodes resulting from vasodilation.[87]

Table 3. Clinical trials on the effect of PBMT in the treatment of COVID-19 and post-COVID-19 complications

Study/region	Patient/groups	Intervention	Outcomes	Clinical Trial Identifier
Marchi et al.[77], (2021)/Brazil	30 eligible patients group1: Active PBMT-sMF (n = 15) group2: Placebo PBMT-sMF (n = 15)	PBMT-sMF: - Using a cordless, portable MR5 Activ Pro LaserShower™ device with 20 diodes (including 4 diodes of 905 nm, 8 diodes of 633 nm 8 diodes of 850 nm). - PBMT-sMF applied to 6 sites of the lower thoracic/upper abdominal region and 2 sites of the neck area - The exposure time: 60 s per site Placebo PBMT-sMF: The same device without any emission	Significant differences in: • Diaphragm thickness • Fraction of inspired oxygen • PO_2/fraction of inspired oxygen ratio • CRP levels • Lymphocyte count • Hemoglobin	NCT04386694
Vetrici et al.[75], (2021)/Canada	10 patients group1: standard medical care group2: standard medical care + adjunctive PBMT	The PBMT group received four daily sessions of near-infrared light treatment	Improvement of pulmonary parameters, including: • SMART-COP • BCRSS • RALE • CAP	NCT04391712
Pereira et al.[76], (2021)/Brazil	20 seriously diagnosed patients with COVID-19	Control group: No received the treatment Laser group: received the treatment in five areas (pulmonary area, face, tonsillar fossae, trachea, and bronch)	• Improvement in PaO2 compared to the control group.	-
Marashian et al.[45], (2022)/ Iran	52 mild-to-moderate COVID-19 patients group1: placebo (n = 28) group2: PBM (n = 24)	PBM group: 620-635 nm light via 8 LEDs, twice daily for 3 days + classical treatment Placebo group: similar to the PBM group, but without turning on the devic	Significant decrease in: • IL-6 • IL-8 • TNF-α	IRCT20200616047799N1
Elbannaa et al.[82], (2022)/ Egypt	Two groups of 100 elders PBM group Control group	PBM group: PBM on both lower calf muscles for 4 weeks (808 nm) control group: placebo PBM for 4 weeks	• Suppression of FSS level • Significantly elevated KATZ score	NCT04676074
Ehsani et al.[73] (2023)/Iran	30 COVID-19 patients group1: intervention group2: control group	Intervention group: Five-session program of high-power PBM Control group: placebo PBM	Improving the levels of: • Ferritin • ESR • CRP • IL-6 • O2 saturation • Respiratory rate	IRCT2017070934969N1
Soares et al.[81], (2023)/Brazil	Patients with CRLTTI in 6 distinct groups	PBM in the tongue dorsum and lateral (groups 1, 2, and 3): group1: 660 nm group2: 808 nm group3: association of 660 and 808 nm group4: TLIB-ventral surface of tongue (660 nm) group5: B complex supplementation group6: Sham laser	• No intergroup statistical differences	U1111-1281–7082
Fatemi et al.[74] (2024)/Iran	60 patients group1: 20 subjects group2: 20 subjects group3: 20 subjects	control group: received common treatments group 2: treated with a low-power gallium arsenide laser diode (660 nm) for 7 minutes and 5 days in a row, in addition to standard treatments 5 days Group 3: received common treatments and a low-power diode laser (450 nm)	• Increase in O2 and PO2 in the two laser therapy groups. • PCO2 decreased in the blue laser group • COP score was reduced in all groups	IRCT20111121008146N39
Lim et al.[78], (2024)/Canada	199 eligible patients group1: Control group2: Treatment (36 patients with 0–7 days of symptoms at baseline and 63 patients with 8–12 days of symptoms)	Control group: receiving SOC Treatment group: receiving SOC + PBMT (20 min 2X/day for 5 days and, subsequently, once daily for 30 days)	• Patients with 0–7 days of symptoms recovered significantly faster with PBMT • Patients with symptom duration ≥ 7 days did not show any significant improvement	NCT04418505
Parreira et al.[80] (2024)/Brazil	70 patients with dysgeusia group1: active local and systemic PBM (n = 34) group2: simulated PBM (n = 36)	- Red wavelength was used at 18 spots on the lateral borders of the tongue (3 J per spot), salivary glands (parotid, sublingual, and submandibular glands—3 J per spot), and over the carotid artery for 10 min (60 J) - All patients in both groups received weekly olfactory therapy for up to 8 weeks	• Dysgeusia improvement in both groups. • At weeks 7 and 8, improvement scores were significantly higher in the PBM group than in the sham group ($P = 0.048$)	RBR-2mfbkkk
Pereira et al.[19] (2024)/Brazil	30 patients with COVID-19 group1: PBM1 group2: PBM2 group3: Sham	PBM groups: vest containing 300 LEDs (l = 940nm) over the thoracoabdominal region - Physiotherapy care was performed twice a week for 6 weeks, with FBM previously applied for 15 minutes	• The PBM1 group showed a statistically significant improvement in pulmonary recovery in relation to the PBM2 group	U1111-1294-3064

Table 3. Continued

Study/region	Patient/groups	Intervention	Outcomes	Clinical Trial Identifier
Oliveira et al.[83] (2024)/Brazil	10 patients with long COVID-19 xerostomia PBM group Placebo group	PBM group: standard xerostomia treatment and also a low-intensity PBMT on the cutaneous topography of the salivary glands (a RED LED cluster, 2 J/cm2, 108 J per session, twice a week for 6 weeks) Placebo group: placebo PBMT	• No significant differences between the groups (maybe because of small sample size)	NCT05760092
Campos et al.[85] (2024)/Brazil	40 patients group1: VPBM group2: simulated VPBM	VPBM group: received the treatment of VPBM using the ECCO Reability device (660±10 nm) Sham group: inactive PBM	• Significant differences were observed in pain levels pre- and post-treatment and between the two groups	NCT05430776
Silva et al.[84], (2024)/Brazil	30 patients with post-COVID-19 PF group1: Sham group group2: PBM1 (patients with post-COVID-19 PF) group3: PBM3	Sham group: physiotherapeutic treatment and LEDs off (placebo) PBM1 group: received physiotherapy + PBM PBM2 group: physiotherapeutic treatment + PBM "PBM was applied for 900 s, with optical power of 6 W, power densities of 2.9 mW/cm2, and energy of 2.6 J/cm2."	• Significant improvement in PBM1 in cardiopulmonary recovery compared to the PBM2 • No significant differences between PBM2 and Sham groups	-

PBM: Photobiomodulation; PBMT: Photobiomodulation therapy; ESR: Erythrocyte sedimentation rate; SOC: standard-of-care; CRLTTI: COVID-19 Related Long-Term Taste Impairment; TLIB: Transmucosal Laser Irradiation of Blood; PF: pulmonary fibrosis; VPBM: vascular Photobiomodulation; PaO2: Partial arterial oxygen pressure

It is hoped that through enhanced interdisciplinary collaboration and a deeper understanding of the biological mechanisms underlying PBMT, significant progress can be made toward closing the gap in adjuvant therapies for COVID-19.

Critical Perspectives and Dissenting Opinions

Although current evidence suggests that PBMT may help reduce inflammation and improve oxygenation in COVID-19, concerns remain regarding the clinical strength and reproducibility of these findings. Differences in irradiation parameters, small sample sizes, incomplete blinding, and the concurrent use of supportive therapies limit cross-study comparison and interpretation. In addition, meta-analyses remain limited and heterogeneous, and the absence of standardized treatment protocols and detailed reporting of key light parameters, particularly power density and wavelength, continues to hinder clinical translation. Therefore, large-scale, multicenter, double-blind studies with standardized dosimetry and fully specified parameters are needed before PBMT can be considered a fully evidence-based option for COVID-19 or other inflammatory conditions.

Conclusion

The evidence synthesized in this review underscores the potential of photobiomodulation (PBMT) as a robust adjunctive intervention in COVID-19 management, primarily by modulating key pathophysiological drivers such as hyperinflammation and mitochondrial dysfunction. Furthermore, PBMT shows considerable promise in addressing post-acute sequelae of SARS-CoV-2 (PASC), including pulmonary fibrosis, olfactory dysfunction, and neurological sequelae, through the orchestration of immune responses and the promotion of tissue repair. While clinical data to date indicate a favorable safety profile, the heterogeneity of existing treatment protocols remains a limitation. Consequently, large-scale, randomized controlled trials are imperative to define standardized dosimetry and definitively establish the clinical efficacy of PBMT as a formalized component of the therapeutic armamentarium for COVID-19.

Acknowledgments

The authors thank Zanjan Metabolic Diseases Research Center and Proteomics Research Center, Shahid Beheshti University of Medical Sciences support during this research.

Authors' Contribution

Conceptualization: Masoumeh Farahani, Nasrin Amiri-Dashatan
Data Curation: Nasrin Amiri-Dashatan, Masoumeh Farahani, Rozhina Ghajarbeigi, Mahdis Nazari
Formal Analysis: Mehdi Koushki, Nasrin Amiri-Dashatan, Masoumeh Farahani
Investigation: Mehdi Koushki, Masoumeh Farahani, Rozhina Ghajarbeigi, Nasrin Amiri-Dashatan, Masoumeh Farahani
Methodology: Mehdi Koushki, Rozhina Ghajarbeigi, Mahdis Nazari, Nasrin Amiri-Dashatan, Masoumeh Farahani
Project Administration: Nasrin Amiri-Dashatan, Masoumeh Farahani
Resources: Nasrin Amiri-Dashatan, Mahdis Nazari, Rozhina Ghajarbeigi
Software: Nasrin Amiri-Dashatan
Supervision: Nasrin Amiri-Dashatan, Masoumeh Farahani
Validation: Nasrin Amiri-Dashatan, Masoumeh Farahani
Visualization: Mehdi Koushki
Writing–Original Draft: Mehdi Koushki, Masoumeh Farahani, Rozhina Ghajarbeigi, Mahdis Nazari, Nasrin Amiri-Dashatan
Writing–Review & Editing: Mehdi Koushki, Masoumeh Farahani, Nasrin Amiri-Dashatan

Competing Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical Approval

This research was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.682).

Funding

This work was supported by Proteomics Research Center, Shahid Beheshti University of Medical Sciences (Grant number: 31043).

References

1. Hamdan A, Eastaugh J, Snygg J, Naidu J, Alhaj I. Coping

strategies used by healthcare professionals during COVID-19 pandemic in Dubai: a descriptive cross-sectional study. Narra X 2023;1(1): e71. doi:10.52225/narrax.v1i1.71
2. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727-33. doi:10.1056/NEJMoa2001017
3. Honrubia JM, Gutierrez-Álvarez J, Sanz-Bravo A, González-Miranda E, Muñoz-Santos D, Castaño-Rodriguez C, et al. SARS-CoV-2-mediated lung edema and replication are diminished by cystic fibrosis transmembrane conductance regulator modulators. mBio 2023;14(1): e0313622. doi:10.1128/mbio.03136-22
4. Amiri-Dashatan N, Koushki M, Ghorbani F, Naderi N. Increased inflammatory markers correlate with liver damage and predict severe COVID-19: a systematic review and meta-analysis. Gastroenterol Hepatol Bed Bench 2020;13(4):282-91.
5. Gayvert K, McKay S, Lim WK, Baum A, Kyratsous C, Copin R, et al. Evolutionary trajectory of SARS-CoV-2 genome shifts during widespread vaccination and emergence of Omicron variant. Npj Viruses 2023;1(1):5. doi:10.1038/s44298-023-00007-z
6. Liu LT, Tsai JJ. Unveiling COVID-19 treatment strategies for immunocompromised individuals: therapeutic innovations and latest findings. Int J Rheum Dis 2024;27(1): e14900. doi:10.1111/1756-185x.14900
7. Farahani M, Niknam Z, Mohammadi Amirabad L, Amiri-Dashatan N, Koushki M, Nemati M, et al. Molecular pathways involved in COVID-19 and potential pathway-based therapeutic targets. Biomed Pharmacother 2022;145:112420. doi:10.1016/j.biopha.2021.112420
8. Alves MC, da Silva RC, de Leitão-Júnior SS, de Balbino VQ. Therapeutic approaches for COVID-19: a review of antiviral treatments, immunotherapies, and emerging interventions. Adv Ther 2025;42(7):3045-58. doi:10.1007/s12325-025-03218-3
9. Yang L, Wu C, Parker E, Li Y, Dong Y, Tucker L, et al. Non-invasive photobiomodulation treatment in an Alzheimer disease-like transgenic rat model. Theranostics 2022;12(5):2205-31. doi:10.7150/thno.70756
10. Ventura RD. A review on photobiomodulation therapy for olfactory dysfunction caused by COVID-19. Med Lasers 2022;11(2):72-7. doi:10.25289/ml.2022.11.2.72
11. Wu C, Liu TC, Duan R, Yang L. Photobiomodulation: a potential non-invasive method to alleviate neurological events following COVID-19 infection. Neurosci Bull 2023;39(10):1595-7. doi:10.1007/s12264-023-01064-3
12. Williams RK. The emerging role of photobiomodulation in COVID-19 therapy part II. Med Res Arch 2023;11(8):1-46. doi:10.18103/mra.v11i8.4028
13. de Toledo Telles-AraujoG, de Cruz KM, Preto KA, Araujo-Silva G, Kraychete DC, da Silva Santos PS, et al. Photobiomodulation in the management of persistent olfactory and gustatory dysfunction post-COVID-19: a systematic review. Lasers Med Sci 2025;40(1):283. doi:10.1007/s10103-025-04534-4
14. Oliveira PC, Correia LO, Lopes NM, Suassuna GR, Doty RL, Pinna FR, et al. Efficacy of the adjunctive use of photobiomodulation therapy in olfactory disorders in post-COVID-19 patients: a randomized controlled trial. Braz J Otorhinolaryngol 2025;91(4):101583. doi:10.1016/j.bjorl.2025.101583
15. de Freitas LF, Hamblin MR. Proposed mechanisms of photobiomodulation or low-level light therapy. IEEE J Sel Top Quantum Electron 2016;22(3):7000417. doi:10.1109/jstqe.2016.2561201
16. Hamblin MR. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. AIMS Biophys 2017;4(3):337-61. doi:10.3934/biophy.2017.3.337
17. Nejatifard M, Asefi S, Jamali R, Hamblin MR, Fekrazad R. Probable positive effects of the photobiomodulation as an adjunctive treatment in COVID-19: a systematic review. Cytokine 2021;137:155312. doi:10.1016/j.cyto.2020.155312
18. Soheilifar S, Fathi H, Naghdi N. Photobiomodulation therapy as a high potential treatment modality for COVID-19. Lasers Med Sci 2021;36(5):935-8. doi:10.1007/s10103-020-03206-9
19. Pereira PC, de Lima CJ, Villaverde AB, Fernandes AB, Zângaro RA. Photobiomodulation in the treatment of pulmonary fibrosis after COVID-19: a prospective study. Res Sq [Preprint]. November 25, 2024. Available from: https://www.researchsquare.com/article/rs-5483003/v1.
20. Ramires M, Mattia MB, Tateno RY, Palma LF, Campos L. A combination of phototherapy modalities for extensive lip lesions in a patient with SARS-CoV-2 infection. Photodiagnosis Photodyn Ther 2021;33:102196. doi:10.1016/j.pdpdt.2021.102196
21. Baeder FM, de Albuquerque AC, Corazza PF, Weigert KL, Puricelli E, Pasetti LA, et al. Oral lesions in patients infected with SARS-CoV-2: a case series. Res Soc Dev 2021;10(4): e45410414349. doi:10.33448/rsd-v10i4.14349
22. Pacheco JA, Molena KF, Martins C, Corona SA, Borsatto MC. Photobiomodulation (PBMT) and antimicrobial photodynamic therapy (aPDT) in oral manifestations of patients infected by Sars-CoV-2: systematic review and meta-analysis. Bull Natl Res Cent 2022;46(1):140. doi:10.1186/s42269-022-00830-z
23. Bowen R, Arany PR. Use of either transcranial or whole-body photobiomodulation treatments improves COVID-19 brain fog. J Biophotonics 2023;16(8): e202200391. doi:10.1002/jbio.202200391
24. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of COVID-19 - final report. N Engl J Med 2020;383(19):1813-26. doi:10.1056/NEJMoa2007764
25. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med 2022;386(15):1397-408. doi:10.1056/NEJMoa2118542
26. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. N Engl J Med 2022;386(6):509-20. doi:10.1056/NEJMoa2116044
27. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with COVID-19. N Engl J Med 2021;384(8):693-704. doi:10.1056/NEJMoa2021436
28. Chan ED, Chan MM, Chan MM, Marik PE. Use of glucocorticoids in the critical care setting: science and clinical evidence. Pharmacol Ther 2020;206:107428. doi:10.1016/j.pharmthera.2019.107428
29. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. N Engl J Med 2018;378(21):1965-75. doi:10.1056/NEJMoa1800385
30. Guérin C, Reignier J, Richard JC, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159-68. doi:10.1056/NEJMoa1214103
31. Chen X, Zhang S, Liu H, Zhang Q, Chen J, Zheng Q, et al. Effect of anticoagulation on the incidence of venous thromboembolism, major bleeding, and mortality among hospitalized COVID-19 patients: an updated meta-analysis. Front Cardiovasc Med 2024;11:1381408. doi:10.3389/fcvm.2024.1381408
32. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. BMJ 2020;370: m3026. doi:10.1136/bmj.m3026
33. Fekrazad R. Photobiomodulation and antiviral photodynamic therapy as a possible novel approach in COVID-19 management. Photobiomodul Photomed Laser Surg 2020;38(5):255-7. doi:10.1089/photob.2020.4868
34. Mokmeli S, Vetrici M. Low level laser therapy as a modality to attenuate cytokine storm at multiple levels, enhance recovery,

and reduce the use of ventilators in COVID-19. Can J Respir Ther 2020;56:25-31. doi:10.29390/cjrt-2020-015
35. Jahani Sherafat S, Mokmeli S, Rostami-Nejad M, Razaghi Z, Rezaei Tavirani M, Razzaghi M. The effectiveness of photobiomudulation therapy (PBMT) in COVID-19 infection. J Lasers Med Sci 2020;11(Suppl 1): S23-9. doi:10.34172/jlms.2020.S4
36. Arjmand B, Rahim F. The probable protective effect of photobiomodulation on the immunologic factor's mRNA expression level in the lung: an extended COVID-19 preclinical and clinical meta-analysis. Clin Pathol 2023;16:2632010x221127683. doi:10.1177/2632010x221127683
37. Lee JH, Chiang MH, Chen PH, Ho ML, Lee HE, Wang YH. Anti-inflammatory effects of low-level laser therapy on human periodontal ligament cells: in vitro study. Lasers Med Sci 2018;33(3):469-77. doi:10.1007/s10103-017-2376-6
38. Rosa IF, Peçanha APB, Carvalho TR, Alexandre LS, Ferreira VG, Doretto LB, et al. Photobiomodulation reduces the cytokine storm syndrome associated with COVID-19 in the zebrafish model. Int J Mol Sci 2023;24(7):6104. doi:10.3390/ijms24076104
39. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther 2017;2:17023-. doi:10.1038/sigtrans.2017.23
40. Shamloo S, Defensor E, Ciari P, Ogawa G, Vidano L, Lin JS, et al. The anti-inflammatory effects of photobiomodulation are mediated by cytokines: evidence from a mouse model of inflammation. Front Neurosci 2023;17:1150156. doi:10.3389/fnins.2023.1150156
41. Qiao Y, He H, Jonsson P, Sinha I, Zhao C, Dahlman-Wright K. AP-1 is a key regulator of proinflammatory cytokine TNFα-mediated triple-negative breast cancer progression. J Biol Chem 2016;291(10):5068-79. doi:10.1074/jbc.M115.702571
42. Luo Y, Zheng SG. Hall of fame among pro-inflammatory cytokines: interleukin-6 gene and its transcriptional regulation mechanisms. Front Immunol 2016;7:604. doi:10.3389/fimmu.2016.00604
43. Pasternak-Mnich K, Kujawa J, Agier J, Kozłowska E. Impact of photobiomodulation therapy on pro-inflammation functionality of human peripheral blood mononuclear cells - a preliminary study. Sci Rep 2024;14(1):23111. doi:10.1038/s41598-024-74533-y
44. Kenney AD, Zani A, Kawahara J, Eddy AC, Wang XL, Mahesh KC, et al. Interferon-induced transmembrane protein 3 (IFITM3) limits lethality of SARS-CoV-2 in mice. EMBO Rep 2023;24(4): e56660. doi:10.15252/embr.202256660
45. Marashian SM, Hashemian M, Pourabdollah M, Nasseri M, Mahmoudian S, Reinhart F, et al. Photobiomodulation improves serum cytokine response in mild to moderate COVID-19: the first randomized, double-blind, placebo controlled, pilot study. Front Immunol 2022;13:929837. doi:10.3389/fimmu.2022.929837
46. Wooff Y, Fernando N, Wong JHC, Dietrich C, Aggio-Bruce R, Chu-Tan JA, et al. Caspase-1-dependent inflammasomes mediate photoreceptor cell death in photo-oxidative damage-induced retinal degeneration. Sci Rep 2020;10(1):2263. doi:10.1038/s41598-020-58849-z
47. Wang Y, Huang YY, Wang Y, Lyu P, Hamblin MR. Photobiomodulation (blue and green light) encourages osteoblastic-differentiation of human adipose-derived stem cells: role of intracellular calcium and light-gated ion channels. Sci Rep 2016;6:33719. doi:10.1038/srep33719
48. Jere SW, Houreld NN, Abrahamse H. Photobiomodulation and the expression of genes related to the JAK/STAT signalling pathway in wounded and diabetic wounded cells. J Photochem Photobiol B 2020;204:111791. doi:10.1016/j.jphotobiol.2020.111791
49. de Souza Costa M, Teles RH, Dutra YM, Neto J, de Brito TV, de Sousa Nunes Queiroz FF, et al. Photobiomodulation reduces neutrophil migration and oxidative stress in mice with carrageenan-induced peritonitis. Lasers Med Sci 2018;33(9):1983-90. doi:10.1007/s10103-018-2569-7
50. Zuo X, Ju C, Zhang Z, Wei X, Ma Y, Song Z, et al. Photobiomodulation regulates inflammation and autophagy in spinal cord injury through NLRP3/caspase-1/IL-1β pathway by targeting TLR2. Mol Immunol 2025;182:1-10. doi:10.1016/j.molimm.2025.03.014
51. Latz E. The inflammasomes: mechanisms of activation and function. Curr Opin Immunol 2010;22(1):28-33. doi:10.1016/j.coi.2009.12.004
52. He Q, Hu D, Zheng F, Chen W, Hu K, Liu J, et al. Investigating the nexus of NLRP3 inflammasomes and COVID-19 pathogenesis: unraveling molecular triggers and therapeutic strategies. Viruses 2024;16(2):213. doi:10.3390/v16020213
53. dos Santos Cardoso F, Gonzalez-Lima F, Coimbra NC. Mitochondrial photobiomodulation as a neurotherapeutic strategy for epilepsy. Front Neurol 2022;13:873496. doi:10.3389/fneur.2022.873496
54. Hamblin MR. Mechanisms and mitochondrial redox signaling in photobiomodulation. Photochem Photobiol 2018;94(2):199-212. doi:10.1111/php.12864
55. da Silva Neto Trajano LA, Siqueira PB, de Sousa Rodrigues MM, Pires BR, de Souza da Fonseca A, Mencalha AL. Does photobiomodulation alter mitochondrial dynamics? Photochem Photobiol 2025;101(1):21-37. doi:10.1111/php.13963
56. Dompe C, Moncrieff L, Matys J, Grzech-Leśniak K, Kocherova I, Bryja A, et al. Photobiomodulation-underlying mechanism and clinical applications. J Clin Med 2020;9(6):1724. doi:10.3390/jcm9061724
57. Rupel K, Zupin L, Colliva A, Kamada A, Poropat A, Ottaviani G, et al. Photobiomodulation at multiple wavelengths differentially modulates oxidative stress in vitro and in vivo. Oxid Med Cell Longev 2018;2018:6510159. doi:10.1155/2018/6510159
58. Maghfour J, Ozog DM, Mineroff J, Jagdeo J, Kohli I, Lim HW. Photobiomodulation CME part I: overview and mechanism of action. J Am Acad Dermatol 2024;91(5):793-802. doi:10.1016/j.jaad.2023.10.073
59. Poyton RO, Ball KA. Therapeutic photobiomodulation: nitric oxide and a novel function of mitochondrial cytochrome c oxidase. Discov Med 2011;11(57):154-9.
60. Al Balah OF, Rafie M, Osama AR. Immunomodulatory effects of photobiomodulation: a comprehensive review. Lasers Med Sci 2025;40(1):187. doi:10.1007/s10103-025-04417-8
61. Lee HI, Lee SW, Kim NG, Park KJ, Choi BT, Shin YI, et al. Low-level light emitting diode (LED) therapy suppresses inflammasome-mediated brain damage in experimental ischemic stroke. J Biophotonics 2017;10(11):1502-13. doi:10.1002/jbio.201600244
62. Zupin L, Gratton R, Fontana F, Clemente L, Pascolo L, Ruscio M, et al. Blue photobiomodulation LED therapy impacts SARS-CoV-2 by limiting its replication in Vero cells. J Biophotonics 2021;14(4): e202000496. doi:10.1002/jbio.202000496
63. Zupin L, Clemente L, Fontana F, Crovella S. Effect of near-infrared and blue laser light on Vero E6 cells SARS-CoV-2 infection model. J Biophotonics 2023;16(3): e202200203. doi:10.1002/jbio.202200203
64. Zupin L, Gratton R, Milani M, Clemente L, Fontana F, Ruscio M, et al. Direct inactivation of SARS-CoV-2 by low level blue photobiomodulation LED at 470, 454 and 450 nm. J Biophotonics 2022;15(6): e202100375. doi:10.1002/jbio.202100375
65. Razzaghi MD, Kamani E. Role low-power blue laser with a wavelength of 405 nm in increasing the level of nitric oxide in increasing the resistance of cells to the virus (COVID-19) and its effect on virus (COVID-19) mortality in vitro. OSP J Case Rep 2020;2(3):1-3.
66. Oliveira MC Jr, Greiffo FR, Rigonato-Oliveira NC, Custódio

RW, Silva VR, Damaceno-Rodrigues NR, et al. Low-level laser therapy reduces acute lung inflammation in a model of pulmonary and extrapulmonary LPS-induced ARDS. J Photochem Photobiol B 2014;134:57-63. doi:10.1016/j.jphotobiol.2014.03.021
67. Aimbire F, Ligeiro de Oliveira AP, Albertini R, Corrêa JC, Ladeira de Campos CB, Lyon JP, et al. Low-level laser therapy (LLLT) decreases pulmonary microvascular leakage, neutrophil influx and IL-1beta levels in airway and lung from rat subjected to LPS-induced inflammation. Inflammation 2008;31(3):189-97. doi:10.1007/s10753-008-9064-4
68. da Cunha Moraes G, Vitoretti LB, de Brito AA, Alves CE, de Oliveira NC, dos Santos Dias A, et al. Low-Level Laser Therapy Reduces Lung Inflammation in an Experimental Model of Chronic Obstructive Pulmonary Disease Involving P2X7 Receptor. Oxid Med Cell Longev 2018;2018:6798238. doi:10.1155/2018/6798238
69. Macedo DB, Tim CR, Kido HW, Macedo JB, Martignago CC, Renno AC, et al. Influence of photobiomodulation therapy on the treatment of pulmonary inflammatory conditions and its impact on COVID-19. Lasers Med Sci 2022;37(3):1921-9. doi:10.1007/s10103-021-03452-5
70. Sigman SA, Mokmeli S, Monici M, Vetrici MA. A 57-year-old African American man with severe COVID-19 pneumonia who responded to supportive photobiomodulation therapy (PBMT): first use of PBMT in COVID-19. Am J Case Rep 2020;21:e926779. doi:10.12659/ajcr.926779
71. Williams RK, Raimondo J, Cahn D, Williams A, Schell D. Whole-organ transdermal photobiomodulation (PBM) of COVID-19: a 50-patient case study. J Biophotonics 2022;15(2):e202100194. doi:10.1002/jbio.202100194
72. Raji H, Arjmand B, Rahim F. The probable protective effect of photobiomodulation on the inflammation of the airway and lung in COVID-19 treatment: a preclinical and clinical meta-analysis. Adv Exp Med Biol 2022;1376:29-44. doi:10.1007/5584_2021_665
73. Ehsani F, Bagheri R, Darban M, Hemati M, Bahrami M, Sharafieh F. Effects of photobiomodulation therapy on lung function and inflammatory factors in patients with COVID-19 during acute stage. Photobiomodul Photomed Laser Surg 2023;41(9):483-9. doi:10.1089/photob.2022.0157
74. Fatemi A, Barati M, Razzaghi Z, Fekrazad R, Sheibani F, Kamani E, et al. Effects of intravenous photobiomodulation therapy in the management of patients with COVID-19. Arch Clin Infect Dis 2024;19(1): e140556. doi:10.5812/archcid-140556
75. Vetrici MA, Mokmeli S, Bohm AR, Monici M, Sigman SA. Evaluation of adjunctive photobiomodulation (PBMT) for COVID-19 pneumonia via clinical status and pulmonary severity indices in a preliminary trial. J Inflamm Res 2021;14:965-79. doi:10.2147/jir.S301625
76. Pereira FL, Luchi E, Corassa JM, Rossi FM, da Silva Mendes P, de Castro Roque EA, et al. Use of photobiomodulation therapy for the evolution of immunomodulatory markers and physiological parameters in patients with COVID-19. Int J Dev Res 2021;11(5):47152-7. doi:10.37118/ijdr.21924.05.2021
77. De Marchi T, Frâncio F, Ferlito JV, Weigert R, de Oliveira C, Merlo AP, et al. Effects of photobiomodulation therapy combined with static magnetic field in severe COVID-19 patients requiring intubation: a pragmatic randomized placebo-controlled trial. J Inflamm Res 2021;14:3569-85. doi:10.2147/jir.S318758
78. Lim L, Hosseinkhah N, Van Buskirk M, Berk A, Loheswaran G, Abbaspour Z, et al. Photobiomodulation treatment with a home-use device for COVID-19: a randomized controlled trial for efficacy and safety. Photobiomodul Photomed Laser Surg 2024;42(6):393-403. doi:10.1089/pho.2023.0179
79. Dias LD, Blanco KC, de Faria CM, Dozza C, Zanchin EM, Paolillo FR, et al. Perspectives on photobiomodulation and combined light-based therapies for rehabilitation of patients after COVID-19 recovery. Laser Phys Lett 2022;19(4):045604. doi:10.1088/1612-202X/ac52f5
80. Parreira LF, Pinheiro SL, Fontana CE. Photobiomodulation in the treatment of dysgeusia in patients with long COVID: a single-blind, randomized controlled trial. Photobiomodul Photomed Laser Surg 2024;42(3):215-24. doi:10.1089/photob.2023.0148
81. Cardoso Soares P, de Freitas PM, de Paula Eduardo C, Azevedo LH. Photobiomodulation, transmucosal laser irradiation of blood, or B complex as alternatives to treat COVID-19 related long-term taste impairment: double-blind randomized clinical trial. Lasers Med Sci 2023;38(1):261. doi:10.1007/s10103-023-03917-9
82. Elbanna RH, Mogahed H, Zahran M, Mohamed E. The effect of photobiomodulation versus placebo on functional capacity and fatigability in post COVID-19 elderly. Adv Rehabil 2022;36(3):19-25. doi:10.5114/areh.2022.119900
83. Oliveira SV, Amorim AC, Lima TO, da Silva GL, de Oliveira JR, Rodrigues MF, et al. Exploring photobiomodulation therapy for long COVID xerostomia: a randomized controlled pilot trial. J Adv Med Med Res 2024;36(11):353-66. doi:10.9734/jammr/2024/v36i115647
84. Silva FS, Pereira PC, Villaverde AB, Zângaro RA. Near-infrared photobiomodulation in patients with post-COVID-19 pulmonary fibrosis: 6-minute walk test. IFMBE Proc 2024;126:338-46. doi:10.1007/978-3-031-94921-0_38
85. Campos MC, Schuler SS, Lacerda AJ, Mazzoni AC, Silva T, Rosa FC, et al. Evaluation of vascular photobiomodulation for orofacial pain and tension type headache following COVID-19 in a pragmatic randomized clinical trial. Sci Rep 2024;14(1):31138. doi:10.1038/s41598-024-82412-9
86. Chang CC, Li YH, Chang ST, Chen HH. Impact of intravenous laser irradiation of blood on cognitive function and molecular pathways in long COVID patients: a pilot study. QJM 2025;118(7):481-8. doi:10.1093/qjmed/hcaf050
87. Zand N, Ataie Fashtami L, Shirkavand S. An overview of the possibility of using photobiomodulation therapy COVID-19 in treatment. Journal of Lasers in Medicine 2020;17(5):28-36.