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INSIGHT

# Photobiomodulation: A Potential Non-invasive Method to Alleviate Neurological Events Following COVID-19 Infection

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In the past several months, confirmed cases have surged as many countries have loosened their bans on Coronavirus disease 2019 (COVID-19) epidemic prevention and control. As a respiratory infectious disease caused by a novel coronavirus called SARS-CoV-2, COVID-19 emerged in late December 2019 and lasted for more than three years worldwide [1]. It is characterized by several common clinical symptoms, including high fever, dry cough, dyspnea, and myalgia [2]. Despite worldwide efforts, COVID-19 remains one of the most infectious diseases, with continually evolving viral variants and strong immune evasion [3]. Moreover, although COVID-19 is a self-limited contagious disease, and patients can recover within 1-2 weeks, nearly 20% of confirmed cases develop severe consequences and multiple cardiovascular complications and sequelae [4]. With an increasing understanding of the disease processes, a large body of research has described the neurological manifestations of COVID-19, including headache, dizziness, anosmia, and hypogeusia [3]. Severe neurological symptoms following COVID-19 infection, including anosmia and acute cerebrovascular events (e.g., acute ischemic stroke, acute hemorrhagic necrotizing encephalopathy), suggest the central nervous system is also affected by the Coronavirus SARS-CoV-2 [5]. Multiple mechanisms contribute to the neurovirulence of SARS-CoV-2 in brain tissue. Among the mechanisms that cause neurological manifestations, hypoxia and inflammation-related changes in brain tissue are essential in triggering neurological events [5].

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Earlier studies provided evidence for the virus's interaction with hemoglobin contributing to hypoxia [6]. Notably, in addition to red blood cells, hemoglobin is also detected in neurons, in which neuronal hemoglobin plays a critical role in regulating hypoxic tolerance and neuronal oxygen homeostasis [7–9]. The normal function of neuronal hemoglobin significantly reduces neuronal apoptosis in neurodegenerative diseases [7]. In addition, as one of the most notable complications of COVID-19, acute respiratory distress syndrome (ARDS) causes insufficient oxygen to pass through the lungs into the bloodstream exacerbating neuronal hypoxia [10]. In addition to hypoxia, a large percentage of COVID-19 mortality is due to ARDS induced by severe inflammatory responses (also known as the cytokine storm) [11]. The cytokine storm-associated ARDS causes shortness of breath, decreased blood oxygen levels, pulmonary edema, and lung failure [11]. The inflammatory cytokine storm, known as cytokine storm syndrome (CSS) and the cytokine cascade, is considered to be a potentially fatal immune reaction that contributes to COVID-19-associated mortality [12]. In COVID-19, the cytokine storm refers to the auto-amplifying release of pro-inflammatory cytokines in response to SARS-CoV-2 [12]. Severe COVID-19 cases exhibit significantly higher levels of white blood cells, neutrophils, pro-inflammatory factors, and chemokines than mild and moderate cases [12]. High levels of pro-inflammatory cytokines are also associated with a poor prognosis of COVID-19 [12]. Recent studies have detected a pronounced neuroinflammation in the central nervous system of COVID-19 patients, suggesting a severe disturbance of the brain's immune response [13]. For instance, a recent study found microglial nodules, altered brain T-cell-microglial interactions, astrocytosis, blood-brain-barrier leakage, and axonal damage in COVID-19 patients [13]. Of note, the excessive inflammatory response is particularly detectable around

the small brain vessels, suggesting that the inflammatory response contributes to the cerebrovascular events during and after infection with the Coronavirus SARS-CoV-2. Collectively, these findings suggest approaches targeting neuronal hemoglobin and neuroinflammation may be promising in alleviating cerebrovascular events and promoting recovery from neurological symptoms.

Photobiomodulation (PBM) therapy, also known as low-level laser therapy, is a widely studied non-invasive method with anti-inflammatory and antioxidant properties [7]. It refers to a series of photochemical reactions induced in biological tissue by utilizing low-energy visible (wavelength between 400 and 720 nm) or near-infrared light (wavelength between ~700 and 1000 nm) with an intensity between 5 and 500 mW [7]. Currently, the leading hypothesis to explain how PBM works proposes that mitochondrial cytochrome c oxidase (CCO) is its primary target. According to the hypothesis, the mitochondrial CCO absorbs near-infrared photons and releases nitric oxide (NO) to relieve the inhibitory effects of NO on CCO activity [7]. The displacement of inhibitory NO promotes the efficiency of the electron transport chain and alleviates the release of reactive oxygen species, followed by decreased oxidative damage and inflammation [7]. However, more studies are still required to verify this hypothesis, as evidence suggests that CCO may not be necessary for the effects of PBM at 660 nm [14]. However, cryptochromes, opsins, citrate synthase, and complex III have been proposed to be stimulated by light [14, 15]. Previous studies have demonstrated the anti-inflammatory effects of PBM in brain injuries and neurodegenerative diseases [7, 16]. These anti-inflammatory effects include reducing microglial and astrocyte activation, alleviating excessive release of pro-inflammatory cytokines, and regulating glial cell phenotype polarization [7]. Moreover, our recent study found that neuronal hemoglobin may contribute to the beneficial effects of PBM and plays an essential role in maintaining intraneuronal oxygen homeostasis [7]. PBM treatment significantly preserves mitochondrial function, neuronal hemoglobin, and intraneuronal oxygen homeostasis. *In vitro,* the study further confirmed the neuroprotective effects of PBM by the knockdown of hemoglobin α (the α-globin subunit of hemoglobin). The mitochondrial protection and the maintenance of intraneuronal oxygen homeostasis exerted by PBM are abolished by hemoglobin α knockdown. However, the specific photobiological mechanism of neuronal hemoglobin following PBM treatment remains unknown. More studies are needed to reveal the photobiological mechanisms of action of neuronal hemoglobin in PBM therapy.

As mentioned previously, coronavirus SARS-CoV-2 can interact with hemoglobin, contributing to hypoxia and disrupting oxygen homeostasis. Therefore, the effects of PBM on hemoglobin and intraneuronal oxygen homeostasis may be helpful in alleviating the neurological symptoms following COVID-19 infection. Other properties of PBM therapy may also contribute to alleviating neurological events in COVID-19, including improving mitochondrial function, increasing blood flow, preventing neuronal apoptosis, promoting neurogenesis, and enhancing neuroplasticity. [17]. However, more studies are still needed.

Indeed, a clinical trial has been performed recently [18]. This study confirmed that PBM alleviates the cytokine storm within 3-10 days and reduces the serum pro-inflammatory cytokines, including TNF-α, IL-6, and IL-8, within 24-72 h [18]. Although this study did not measure the effects of PBM

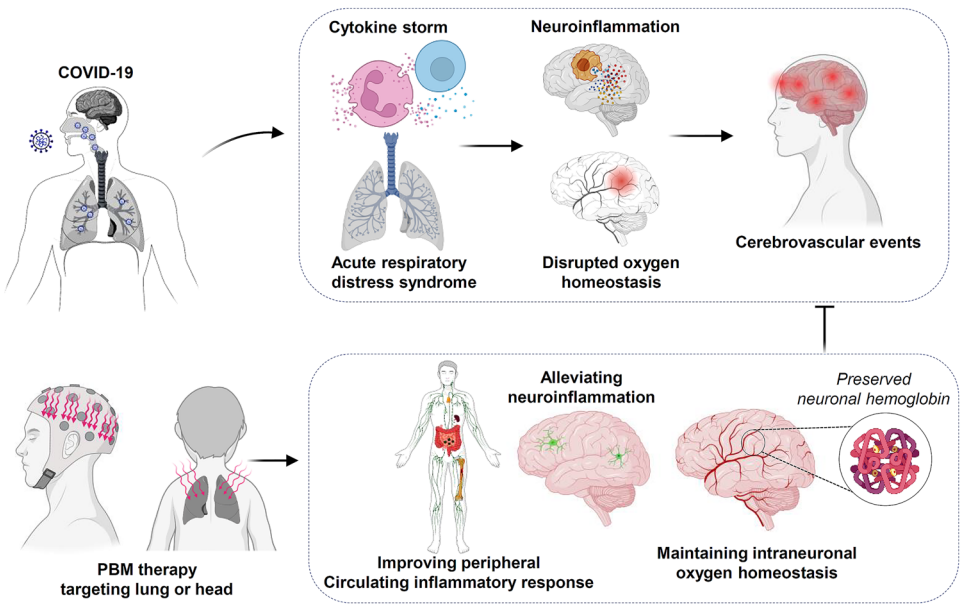


**Fig. 1** PBM may alleviate neurological events following COVID-19 infection by targeting inflammatory responses and oxygen homeostasis. Hypoxia caused by Coronavirus SARS-CoV-2 infection and inflammation-related changes in brain tissue are essential in triggering cerebrovascular events. PBM targeting the lung or head could alleviate the cytokine storm and maintain intraneuronal oxygen homeostasis by preserving neuronal hemoglobin.

on inflammatory responses in the CNS, the improvement in the peripheral circulating inflammatory response suggests promising anti-inflammatory effects of PBM on the CNS.

In conclusion, the anti-inflammatory effects of PBM in brain disorders and evidence from the clinical trial on the peripheral circulating inflammatory response following COVID-19 support the promising use of PBM in alleviating cerebrovascular events during and after infection with the Coronavirus SARS-CoV-2. Of note, in addition to investigating the anti-inflammatory role of PBM, the effects of PBM on brain hypoxia also deserve further investigation. Notably, the efficiency of PBM therapy depends on multiple parameters simultaneously, including wavelengths, durations, target area, intensities, and operation mode [16]. Both pulsed and continuous wave light at 400-1000 nm wavelength with a power between 5 and 500 mW could be further investigated in COVID-19 therapy. In a nutshell, according to the biological properties of PBM and evidence from previous studies, we conclude that PBM is a potential non-invasive method to alleviate cerebrovascular events following COVID-19 infection. It would be interesting to investigate whether PBM targeting the lung or head could reduce the occurrence of acute ischemic stroke or promote recovery from neurological symptoms following COVID-19 infection (Fig. 1). Looking deeper into the mechanisms underlying the effect of PBM on the CNS may shed light on preventing and rehabilitating neurological symptoms during the COVID-19 pandemic.

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**Competing interests** The authors declare that they have no competing interests

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