Photobiomodulation Therapy and COVID-19

Subjects: Infectious Diseases
Contributor: Rogerio Buchaim

COVID-19 is a viral disease characterized as a pandemic by the World Health Organization in March 2020. Since then, researchers from all over the world have been looking for ways to fight this disease. Many cases of complications arise from insufficient immune responses due to low immunity, with intense release of pro-inflammatory cytokines that can damage the structure of organs such as the lung. Thus, the hypothesis arises that photobiomodulation therapy (PBMT) with the use of a low-level laser (LLLT) may be an ally approach to patients with COVID-19 since it is effective for increasing immunity, helping tissue repair, and reducing pro-inflammatory cytokines. This systematic entry was performed with the use of PubMed/MEDLINE, Web of Science, Scopus and Google Scholar databases with the following keywords: "low-level laser therapy OR photobiomodulation therapy AND COVID-19".

Keywords: COVID-19 ; SARS-CoV-2 infection ; immunity ; inflammation ; low-level laser therapy ; photobiomodulation therapy ; systematic review

1. Introduction

COVID-19 (SARS-CoV-2) is a viral disease discovered in December 2019, in the Chinese city of Wuhan, and spread to several continents, which led the World Health Organization (WHO) to characterize the disease as a pandemic 11 March 2020 [1]. This fact demonstrates the considerable speed of propagating this infectious pathogen, spreading around the world in a few months because on average, one infected person spreads the infection to three other people [2]. The forms of contamination are varied, such as through droplets of saliva, contaminated objects and surfaces, coughing, and sneezing. Thus, social distance and hygiene measures are essential to reduce contamination by the virus, with social isolation being the most effective method [3][4].

The most common symptoms of COVID-19 are cough, fever, anosmia, ageusia, difficulty breathing, and in more severe cases, pneumonia. Some conditions, such as diabetics, cardiac and hypertensive individuals, are more susceptible to presenting more severe conditions. This is also observed in people with low immunity since immunity is a great ally to the fight against coronavirus in the human body [5][6].

However, although high immunity is a good ally, its low levels can intensify the inflammation process. In the case of a defective immune response against COVID-19, an accumulation of immune cells in the lungs can occur, causing an exacerbated production of pro-inflammatory cytokines, which can damage the lung structure. With this excess of cytokines, it can spread to other locations, causing damage to multiple organs. In a healthy immune response, virus-specific T cells target inflammation and eliminate infected cells, preventing the virus from spreading, leading to minimal damage. Thus, stimulation of immunity is critical to approach the new coronavirus [7].

There are several ways to increase immunity that can be conducted by practicing physical activity and having good eating habits, which have been shown to affect immune sensitivity and inflammation [8]. There is also the possibility of using Vitamin D and Zinc in capsules, which in the body have beneficial immunomodulatory and anti-inflammatory effects in infections caused by viruses. Still, in the context of COVID-19, there is no scientific evidence to prove the effectiveness of these elements [9].

Another way of modulating the immune system is the use of photobiomodulation therapy (PBMT), which can stimulate immune cells to clump together at the site of the affected cells and assist them in survival through greater anti-inflammatory cytokine expression and decreased pro-inflammatory. In precursor studies, it was observed that laser light in low doses accelerated the healing of excisional wounds, called laser biostimulation [10]. There was a clear lack of consensus on the terminology for this therapy. The term most often used is low-level laser therapy (LLLT). ‘‘Laser’’ is not the most appropriate term as other light devices such as LEDs are currently used for this application. The ideal term and its definition must be precise and emphasize its scientific basis, with photobiomodulation being the term of choice to describe this use, meaning light therapy that uses non-ionizing forms of sources including lasers, LEDs, and broadband light in the spectrums visible and infrared [11].

The effect of PBMT is due to its absorption by tissues through photoreceptors, facilitating events such as mitochondrial respiration, calcium transport—which results in more significant cell proliferation—repairing, and regenerating tissues [12][13][14][15]. PBMT has to assist in the recovery process from nerve [16][17][18], bone [19][20][21], respiratory tract [22][23][24][25], and other injuries involved in functional rehabilitation, favoring the patient's recovery. LLLT can be used with the ILIB technique (Intravascular Laser Irradiation of Blood), which increases immunity, inducing positive effects on the expression of immunoglobulins (IgA, IgM and IgG) and modulation of inflammation. Therefore, this technique can be used to treat various pathogens such as infectious diseases, bronchitis, and pneumonia [26].

2. Selections of Study

The phases of the bibliographic search were organized by the Prisma Flow Diagram [27] (Figure 1).

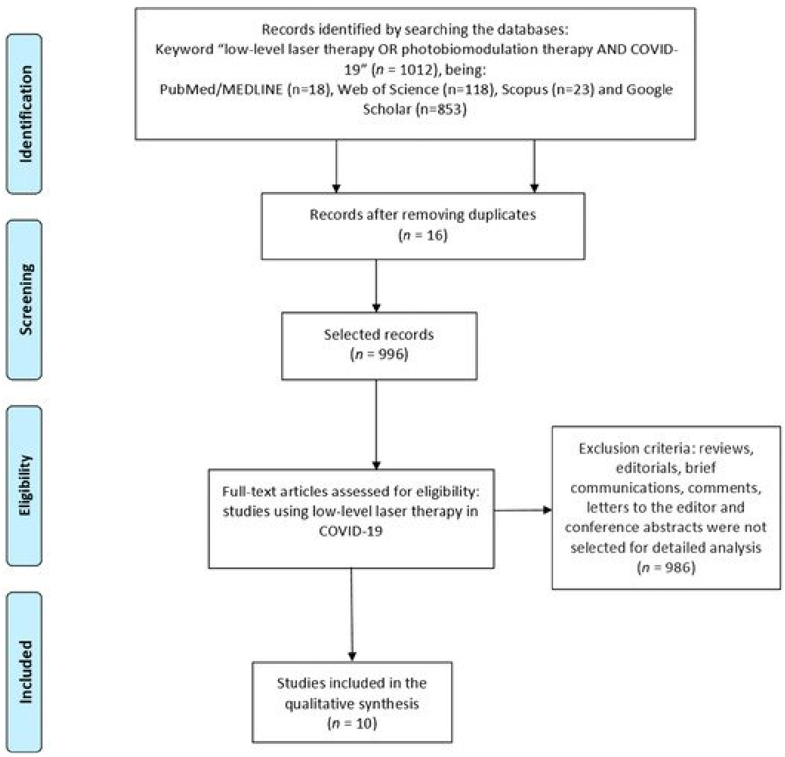

Figure 1. Flow diagram showing the study selection [27].

3. Photobiomodulation Therapy as a Possible New Approach in COVID-19

This systematic review was carried out to evaluate the published literature, against the established descriptors and the inclusion and exclusion criteria of the articles, in an attempt to identify patterns and trends on the association of COVID-19 and PBMT, as well as to identify possible gaps and trends new areas of research. Although there are still few studies, our results shown that PBMT can bring benefits for COVID-19 patients since it is related to modulating the immune system, to the reduction of inflammation, and other beneficial activities for the restoration of health.

SARS-CoV-2 leads to the death of cells attacked by it, causing a blockage in the airways with its waste, making breathing more difficult with the accumulation of dead cells and fluids in the lungs [28]. The immune reaction in the infected patient usually causes inflammation and fever. With vasodilation at the site of infection, the lungs accumulate fluid [29]. This exaggerated immune response is called cytokine storm, which causes Acute Respiratory Distress Syndrome (ARDS), fever, multiple organ failure, and death [30]. The effect of laser therapy is related to the amount of laser energy per cm^2. The minimum therapeutic dose for a biostimulant effect for the red and infrared laser is 0.01 J/cm^2, while for the blue, ultraviolet, and green lasers it is 0.001 J/cm^2. The effective stimulation dose is 1 J/cm^2 and doses greater than 10 J/cm^2 can produce inhibitory effects, used in conditions that require inhibition and suppression, such as, for example, suppressing the inflammatory response in an attempt to avoid or minimize the storm of pro-inflammatory cytokines [30].

The use of phototherapy in treating illnesses has been reported since Ancient Greece, initially called Heliotherapy, and consisted of leaving the sick exposed to the sun to cure their ailments, as shown in Table 1 [31]. In 1918, during the crisis caused by the Spanish flu, phototherapy proved to be a great ally in the treatment of this disease, being pointed out as one of the most significant factors in reducing mortality. Since then, several studies have been carried out to understand better the beneficial effects of light, especially blue, violet, red, and infrared light [31].

These studies found blue and violet light effects such as virus inactivation, including coronavirus and the common flu virus, and antimicrobial effect. These effects can be used, respectively, for cleaning, avoiding contagion by a coronavirus from infected surfaces, and mitigating opportunistic bacteria in the treatment of COVID-19 [31][32][33]. In addition, therapeutic effects of red and infrared light have also been found effective in treating various diseases such as pneumonia, decreasing inflammation, pulmonary edema, and fibrosis in the lung. These effects are important to avoid many complications of COVID-19, with ARDS the leading cause of death from the disease [31]. From this, more technological and specific lasers were developed, giving rise to photobiomodulation, which can be a great ally to the treatment of COVID-19.

Moreover, the effects of the blue laser go beyond the antimicrobial and anti-inflammatory capabilities. Its irradiation in the blood also favors hormonal harmonization, pain reduction, and the release of hemoglobin nitric oxide (HbNO), which has a powerful antibacterial effect and causes the destruction of microorganisms of all types in the blood. This can be used in antimicrobial photodynamic therapy with the combination of Riboflavin, a photosensitizer, for bacterial, viral, and parasitic diseases. The production of nitric oxide (NO) in the immune system is key to the capabilities and characteristics of immune cells and having cytotoxic and cytoprotective, antiviral, antimicrobial effects, and stimulating and suppressing the immune system. With the blue laser increasing the level of NO, mitochondrial biogenesis in different types of cells and oxygen connection to red blood cells is also increased (Figure 2) [5][34][29]. However, the use of lasers in viral mortality is not widespread, but there is evidence that the 405 nm LED light has antiviral activity [31]. Thus, the coronavirus could be killed or altered to be used in the preparation of vaccines. For this, the maximum irradiation takes 10 min with a power of 2 mW [5][34].

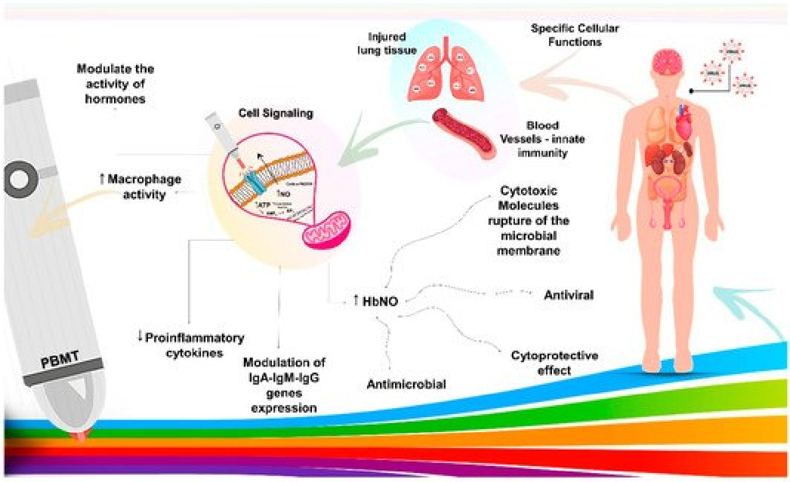

Figure 2. The schematic diagram illustrates COVID-19 infection in the human body, followed by rapid spread from viral sanctuary sites. Early innate host immune response dictates viral load at the acute phase. Photobiomodulation therapy (PBMT) acts on transmembrane receptors present in the mitochondria with specific cellular functions, modulating cells with functional deficits, such as blood cells and lung tissue, promoting signaling by the absorptivities of electromagnetic rays. These chromophores convert electromagnetic energy into adenosine triphosphate, and then induce increased macrophage activity, modulation of plasma hormone levels, decreased proinflammatory cytokines, modulated expression of IgA, IgM, and IgG immunoglobulins, and increase of the HbNO synthesis. The results are positive with the synthesis of cytotoxic molecules to microbial membranes, which leads to the destruction of microorganisms of all types in the blood and cytoprotective effect to human cells.

Since the onset of the disease, there is a consensus among clinicians and researchers about the role of the SARS-CoV-2 virus in pulmonary complications, which can lead to a severe respiratory syndrome. Nitric oxide (NO) is beneficial in low concentrations, but it can produce reactive nitrogen species (RNS), such as peroxynitrite, in high concentrations. Both ROS (species that react to oxygen) and RNS are destructive at high doses. In pulmonary inflammation, the increased influx of neutrophils produces high levels of ROS and RNS, damaging the lung tissue (Figure 2). PBMT can reduce ROS formation [35][36], reduce pulmonary edema, neutrophil influx, and promote lung tissue regeneration and better oxygenation to all related organs [37].

As for the type of laser, infrared is preferred due to the greater capacity of penetrating the lung tissue [38]. The dosimetry of adequate energy density is 9.5–10.5 J/cm^2. Continuous irradiation at different points in the respiratory system can be helpful in the treatment of COVID-19 pneumonia. PBMT can be used as a preventive approach in high-risk, elderly, or comorbid patients receiving pre-treatment PBMT while still at an early stage of the disease [32]. In addition, PBMT can be considered a therapeutic approach in hospitalized patients before their condition worsens enough to require ICU admission [37].

Moreover, in addition to the damage to lung tissues, SARS-CoV-2 also favors the formation of thrombi. Nitric oxide has the potential to treat thrombosis associated with mechanical devices due to its ability to reduce platelet activation and due to the central role of platelet adhesion in device thrombosis [39]. One study, shown in Table 1, reports the effects of nitrite, distant red light, and their combination in various measures of blood clotting using a variety of agonists. The authors concluded that the combination of extreme red light and nitrite treatment decreased the coagulation measures in all cases [39]. It is believed that the radiation from the infrared laser near the red (R/NIR) can stabilize the membrane of red blood cells (RBC) by increasing its resistance to destructive factors, reducing trauma in the use of equipment, such as extracorporeal circulation [33].

Likewise, there are techniques for increasing the efficiency of light, such as PDT, since its penetration into tissues is limited. One technique is the association of PDT with phototherapy agents, which sensitize specific molecules to absorb light better. PDT has been clinically validated in several esophageal pathologies and some lung cancers and can be used to destroy pathogenic microorganisms such as bacteria and viruses [31][40]. This can also be seen in the association of PDT with Phthalocyanines, a phototherapeutic agent that makes incorporation by target cells easier. The use of phototherapeutic agent Phthalomethyl D shows promising effects if used with the aim of leading to immunological improvement, cure, and repair against viral induction [41].

In this scenario, with the use of PDT by the ILIB technique through radial artery for 30 min at a wavelength of 660–460 nm, 100 mW output power, and in continuous wave mode for point irradiation (Ecco Fibras, São Paulo, SP, Brazil) and the use of Phthalomethyl D administered orally or introduced into the digestive tract, wound healing and the systemic inflammatory process were improved. It can be suggested that, at low doses, phagocytic activity increases, and cell viability decreases after the execution of this technique. Thus, the relationship between the action of the laser and the activation of monocytic cells may explain the process of resolving systemic inflammation with more efficient wound closure. Thus, its contribution to the anti-inflammatory response during viral infection may be an approach to SARS-CoV-2 [41].

Clinical study using PDT in 300 patients, methylene blue (MB) photosensitizer and 660 nm red light applied in the oral and nasal cavity, compared to placebos, led to significant decreases in morbidity and reduced mortality rates, contributing to the immune response [42]. In vitro, PDT with MB and Radachlorin, using continuous laser with wavelength 662 nm at doses of 16 J/cm^2 and 40 J/cm^2 of laser irradiation, shows high antiviral activity against SARS-CoV-2 [43].

Furthermore, COVID-19 mainly attacks the lung and heart tissues. This is because the coronavirus binds to the cell through the angiotensin-converting receptor, which is highly expressed in lung and heart cells. Thus, it is vital that the receptor is not available to bind to the coronavirus, and for that, Vitamin D, which also binds to that receptor, can help. There are no acute cases of heart attack at balanced levels of Vitamin D due to COVID-19 [44]. In addition, Vitamin D has a broad spectrum of immunomodulatory, antifibrotic, anti-inflammatory and antioxidant actions [9][45].

One of the safest ways to increase Vitamin D levels in the body is the use of the 50 mW 589 nm yellow laser, which can be applied through the nose or acupuncture points (acupuncture laser) [44]. In addition, Vitamin D deficiency has been found, to be related to increased mortality and disease progression. It was also observed that the expression of inflammatory cytokines was inhibited by Vitamin D, and its insufficiency was related to the overexpression of cytokines and that it plays an important role in cardiovascular diseases and diabetes mellitus, risk factors for the disease [38]. Therefore, ways to obtain good Vitamin D levels in the body can be a preventive approach to complications of COVID-19 [44][45].

In severe SARS-CoV-2 infections, recent histopathological studies have emphasized the important role of Endothelial Cells (EC) in immune-thrombosis, vascular dysfunction, and inflammation. The storm of pro-inflammatory cytokines, commonly seen in irregular immune responses, can also cause endothelial dysfunction (EnD). The endothelitis caused by COVID-19 can explain the impairment of the systemic microcirculatory function of different organs and is highly harmful [46]. The endothelium performs multiple functions, such as regulating the transport of biologically active substances, barrier, participation in phagocytosis, and control of the diffusion of fluids, electrolytes, metabolic products, and platelet adhesion. Therefore, EnD can be catastrophic, becoming a primary cause of high mortality and the development of diseases or complications that disrupt a fully human life, so preventing the development of EnD is paramount [47][46].

Thus, with LLLT, at the systemic level, it is possible to activate microcirculation and metabolism, better regeneration of lung tissue, increased local immunity, and improved muscle support for the respiratory act. As a result, laser illumination using the ILIB technique has been widely used to correct endothelial function. The “classic” way of using this method is with a wavelength of 635 nm, 2–3 mW of lighting power at the fiber outlet, 10–20 min of exposure. With this technique, in seven daily sessions, patients with mild illness (six people) achieved an overall improvement in health, relief of chest pain during cough, and improvement in sputum discharge due to the increased effectiveness of the cough impulse [47][48].

One patient, with a severe disease course, used five combined laser therapy procedures: ILBI-525 intravenous laser blood illumination + LUVBITM violet laser ultra-blood illumination (525 nm wavelength, green spectrum, 2 mW lighting power, 5 min exposure per zone + 365 nm wavelength, UV spectrum, 2 mW of illumination and 5 min exposure per zone on alternate days) and exposure to pulsed IR LLLT (904 nm wavelength with light pulse duration of 100 ns, pulsed power of 15 W, power density of 10–15 W/cm^2, frequency of 80 Hz and 1.5 min of exposure). With this approach, in the fifth procedure, the patient noticed a significant improvement in general health and the disappearance of shortness of breath with moderate physical effort [47][48][49].

Knowing that LLLT is effective against the cytokine storm and ARDS, promoting tissue healing and regeneration, experimental models in animals have shown a decrease in inflammation without impairing lung function in the case of acute lung injuries, which could be an approach to pulmonary inflammatory diseases [25]. In this experimental study, the effect of LLLT on chronic obstructive pulmonary disease was evaluated. The results demonstrated that LLLT significantly reduced the number of inflammatory cells and the secretion of pro-inflammatory cytokines as IL-1 β, IL-6, and TNF-α in bronchoalveolar lavage (BAL). It was also observed that LLLT decreased collagen deposition and the expression of the purinergic P2X7 receptor. Thus, LLLT is considered a promising treatment for other lung diseases, such as COVID-19 [25].

In addition, prolonged time on ventilators causes lung injuries, which can further aggravate the disease. For this, the use of LLLT is shown to minimize this side effect. This was proven in experimental models of ventilator-induced lung injury in rats, and with the use of LLLT there was an anti-inflammatory effect via decreased lung injury scores and lower neutrophil counts in alveoli, interstitial, and bronchial lavage [35]. Modulation of inflammatory factors and a drive for healing are needed to help patients get off the ventilators. Thus, LLLT is a safe and non-invasive technique that has been used for decades in the treatment of pain, wound healing, and health conditions, including diseases of the respiratory system. LLLT combined with standard medical care to optimize response to treatments, reduce inflammation, promote healing, and speed recovery times is a promising approach [30].

Another technique that can be useful in this scenario is PBMT when used alone or combined with the static magnetic field (PBMT-sMF). In a study, with patients with severe COVID-19 that required mechanical ventilation were randomly assigned to receive PBMT-sMF (six sites on the lower chest—189 J in total and two sites in the neck area—63 J in total) or PBMT-sMF placebo daily for the entire ICU stay, it was noted that PBMT-sMF was able to improve some ventilatory parameters, in addition to the infectious process, and immune response [50]. Thus, these techniques suggest that treatment with PBMT-sMF or LLLT may reduce the burden on the hospital and health systems and the use of scarce health care resources during this pandemic [30][50].

PBMT techniques in the hospital were observed in the clinical case of patient with severe COVID-19 [51]. This was the case of a 32-year-old Asian woman with morbid obesity and a body mass index of 52, and a history of excision of meningioma and asthma presented to the emergency room with a positive COVID-19 test and shortness of breath, cough, and diarrhea. The patient presented hypoxia with oxygen saturation via pulse oximetry (SpO2) of 88% in room air, tachypneic with a respiratory rate of 35, feverish temperature of 100.5 ºF, pulse rate 89, and blood pressure 106/84. The condition was considered severe, and was worsened, leading to her admission to the ICU. As a result, treatment with LLLT was started. During the first laser treatment, her SpO2 increased from 92% to 97% at 3 L/min of oxygen within 10 min of starting treatment. After the second laser treatment, the patient was breathing without dyspnea. After treatments, her respiratory rate returned abnormally 19–20 breaths/min. After the fourth treatment, the patient was able to ambulate independently and improved the ability to perform activities of daily living. The patient was discharged two days after her last treatment with 1 L/min of oxygen [51].

Another case was that of a 57-year-old African American man with severe COVID-19 who received four sessions of PBMT once a day by a laser scan and with pulsed modes of 808 nm and super pulses of 905 nm for 28 min [52]. Oxygen saturation (SpO2) increased from 93–94% to 97–100%, while oxygen demand 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 indium (Brescia-COVID and SMART-COP) decreased from 4 to 0. CRP normalized from 15.1 to 1.23. This patient tolerated all 4 treatments daily and observed a significant improvement in breathing immediately after each treatment. Paroxysmal coughing fits were resolved after the third treatment. Upon completion of the fourth treatment, the patient was able to ambulate with physical therapy. The next day after his final treatment, the patient was discharged to an acute rehabilitation facility with oxygen at 1 L/min [52].

Perhaps soon, the results of clinical trials currently underway should contribute to the assessment of PBMT efficacy for improving respiratory, inflammatory, coagulation and morbidity-mortality parameters in patients undergoing these studies.

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