Review Article

ISSN: 1735-0344 *Tanaffos 2023; 22(3): 279-289*

TANAFFOS

Light-Based Therapy: Novel Approach to Treat COVID-19

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Received: 8 August 2022
Accepted: 1 February 2023

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The pandemic outbreak of Coronavirus disease 2019 (COVID-19) which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), is a new viral infection in all countries around the world. An increase in inflammatory cytokines, fever, dry cough, and pneumonia are the main symptoms of COVID-19. A shared of growing clinical evidence confirmed that cytokine storm correlates with COVID-19 severity which is also a crucial cause of death from COVID-19. The success of anti-inflammatory therapies in the recovery process of COVID-19 patients has been well established. Over the years, phototherapy (PhT) has been identified as a promising non-invasive treatment approach for inflammatory conditions. New evidence suggests that PhT as an anti-inflammatory therapy may be effective in treating acute respiratory distress syndrome (ARDS) and COVID-19. This review aims to a comprehensive overview of the direct and indirect effects of anti-inflammatory mechanisms of PhT in ARDS and COVID-19 patients.

Keywords: Photobiomodulation; Photodynamic therapy; Ultraviolet therapy; COVID-19; Anti-inflammatory

INTRODUCTION

In December 2019, a cluster of severe pneumonia was discovered in Wuhan, China, which can present with acute symptoms of fever, dry cough, and weakened immune system with a decrease in white blood cells (1). The novel coronavirus is a severe disease that leads to acute respiratory distress syndrome (ARDS) and has been attributed to cytokine release syndrome (CRS) (2). In various studies, a strong association has been reported between severity and cytokine storm (3). CRS in severe COVID-19 patients and immunodeficiency disease causes ARDS (4, 5). Cytokine storm also known as cytokine storm syndrome (CSS) is a hyperactive immune response that is associated with the release of interferon (IFN), interleukins (IL), tumor necrosis factors (TNF), chemokines, and several other inflammation mediators. High levels of cytokines released in the CSS process are injurious to host cells (6). To date, no definitive antiviral treatment has been reported for this disease. However, preventive treatment is necessary for patients. Some monoclonal antibodies targeting interleukin (IL-6) activity such as tocilizumab and sarilumab, use as a drug to treat COVID-19 patients (7-10).

Photobiomodulation Therapy (PBM) also known as low-level laser therapy (LLLT), is a kind of laser therapy that uses visible light and near-infrared light by the photochemical reaction in the cell process (11-13). PBM as a treatment has significant anti-inflammatory effects in reducing pain, improving lymphedema, wound healing, and musculoskeletal injuries (14). Recent studies have shown promising results of PBM in reducing acute pulmonary inflammation. Thus, the use of PBM can be an effective therapy for ARDS management in COVID-19 patients (14-16). Also, PhT therapy has been identified as a non-invasive treatment for inflammatory conditions (17). This review aims to report several direct and indirect

effects of PBM on the treatment of COVID-19 and ARDS patients.

PBM Therapy

PBM is a non-invasive intervention treatment strategy that uses a low-intensity light source, such as light amplification by stimulated emission of radiation (LASER) or light-emitting diode (LED) (18). A suitable light source for PBM should be non-ionized and non-thermal in the visible and infrared spectrum (600-1200 nm) which in turn reduces inflammation and stimulates healing (19). Experimental studies showed that PBM-based therapy can affect mitochondria and lead to the release of molecules such as ATP, cAMP, NO, and ROS, which causes cells to modulate oxidative stress and have an antioxidant effect (20). Optical energy absorbed by intracellular light receptors causes a cascade of photochemical intracellular signaling that improves cellular activity and increases the patient's healing process (21, 22). PBM therapeutic can reduce cellular stress via stimulating anti-inflammatory enzyme activity (23). However, PBM has shown significant anti-inflammatory effects in reducing pain, improving lymphedema, wound healing, and musculoskeletal injuries (14) (Figure 1).

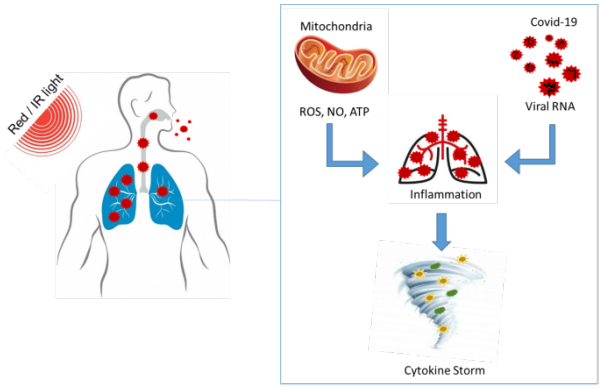

Figure 1. PBM mechanism on lung inflammation in COVID-19 patient

The first line of defense against viral infection is the innate immune response (24). Destruction of lung cells and COVID-19 infection cause absorption of monocytes and macrophages to increase immune responses by producing adaptive T and B cells and prepared proinflammatory interleukins (IL1β, IL-6), IFN, C-C Motif chemokine ligands (CCL2, CCL3, CCL5), and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-kB) from dendritic cells (DCs) and macrophages. (14, 25). Altogether, in viral infection, viruses enter the host cells which are recognized by Pattern Recognition Receptors (PRR) expressed by local cells of the innate immune response such as macrophages (26, 27). This ligand binding leads to the activation of transcription factors such as interferon regulatory factors (IRF), NF-kB, and AP-1 to produce antiviral INF (Type-I, Type-II) and others (28). On the other hand, increasing chemokines leads to an increased innate immune response through attracting monocytes, NK cells, and DCs to target virally infected cells (29). The recent result shows that coronavirus infection leads to induce the response of various types of interferon (INF-I, INF-II, INF-III) and exaggerated activation of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. Besides this, reports indicate an increased accumulation of inflammatory monocyte-macrophage and neutrophil in the bronchoalveolar lavage (BAL) and lung of COVID-19 patients. Notably, high levels of IL-6 have been observed in COVID-19 mortality (30, 31). Also, rise in proinflammatory cytokines and chemokines such as IL-2, IL-7, IL-10, Tumor Necrosis Factor-alpha (TNF-α), macrophage inflammatory protein-1-alpha (MIP1α), Interferon-gamma-induced protein10 (IP10), monocyte chemoattractant protein 1 (MCP1), and granulocyte-colony stimulating factor (G-CSF), all the hallmarks of COVID-19 patient serum, increases with the progression of the viral infection (32, 33).

PBM as one of the non-invasive tools well-known as LLLT which uses near-infrared light in the range of 450–1000 nm with anti-inflammatory effects may be an allied approach to patients with COVID-19 to reduce pro-inflammatory cytokines (15), and increase immunity response and tissue repair. Studies in several cases of COVID-19 patients have shown that PBM therapy reduces

inflammatory markers and improves radiological symptoms in patients. It is also used as a prophylactic treatment against coronavirus (34, 35). PBM radiation significantly increases cell viability and on the other hand, reduces mRNA expression of proinflammatory cytokines, TNF-α, and IL-1β. According to recent studies, PBM improves lung tissue repair and oxygen depletion by reducing pulmonary edema (36) and neutrophil infiltration.

Using infrared lasers as an important part of PBM therapy in the treatment of COVID-19 have a greater ability to penetrate the lung tissue, with appropriate dosage and density. Directly applying continuous infrared laser radiation on different parts of the respiratory system can increase the coronavirus recovery process. As mentioned, PBM can act as a preventative measure in patients with coronavirus in the early stages of infection. Also, PBM may be considered as a treatment for hospitalized patients before they worsen to be admitted to the ICU. Therefore, randomized clinical trials on the effects of PBM on COVID-19 should be performed, although some have already begun in different parts of the world (37).

In PBM therapy, the energy of the photons is absorbed directly by cytochrome c oxidase (COX). By absorbing photonic energy by COX in the mitochondria, it acts as a generator of ROS (reactive oxygen species) and increases the activity of the entire electron transport chain, eventually producing more adenosine triphosphate (ATP) (38).

NF-KB (nuclear factor Kappa-B), which plays a main role in cell signaling pathways, interacts with ROS. NF-KB is transported to the nucleus and affects the expression of many genes (more than 150 genes). Many genes are involved in defense mechanisms against inflammatory responses, anti-apoptosis, cell migration, and cell survival (39). Researchers reported that PMB cellular mechanisms are regulated by the Toll-4 receptor signaling pathway (TLR4) and ROS activation, and eventually, induce NF-KB factor and increase the level of pro-inflammatory cytokines such as IL-6, IL-1β, and IL-8 (40). It was noteworthy that stimulation of light and the presence of a magnetic field act as non-invasive therapies to produce anti-inflammatory effects and regulate ROS signaling pathways in COVID-19 patients (40). They reported that daily exposure to two 10-minute intervals of moderate-intensity infrared light significantly reduced the inflammatory response of the TLR4 receptor signaling pathway in human cells. Exposure to the electromagnetic field of cells at 10-minute intervals daily or from pulsed electromagnetic fields (PEMFs) intensifies their anti-inflammatory properties (41).

Effect of PBM on Acute Pulmonary Inflammation

With the treatment of cytokine storm, PBM has a double effect on tissue repair. It has shown a good effect on the treatment of allergic lung inflammation, vocal fold injuries, periodontitis, and oral lesions through its anti-inflammatory and regenerative features (42, 43).

Experimental and animal models of lung disease and infection have revealed numerous cellular and molecular effects that are both local and systemic. Recent studies have shown that PBM may be a low-cost and effective option for the treatment of inflammatory and fibrotic diseases (44). Studies show the effect of PBM on acute inflammatory diseases of the lungs in COVID-19 patients (37). It reduces acute lung injury and pulmonary inflammation and is a promising therapeutic approach for inflammatory lung diseases (45).

An increased number of polymorph nuclear neutrophils (PMNs) in the interstitial space and release of some pro-inflammatory cytokines including IL-1β, IL-6, IL-8, TNFα, MCP-1, and MIP-1 has been observed in acute pulmonary inflammation (46). In patients with acute inflammation in COVID-19, delivered PBM to the trachea can reduce pulmonary vascular leakage in MIP-2 mRNA expression, IL-1b levels, and intracellular ROS production. PBM reduces the influx of neutrophils by inhibiting COX-2-derived metabolites, leading to a reduction in inflammation (47). On the other hand, PBM improves the patient by increasing the apoptosis of inflammatory cells. In a patient with acute lung injury, PBM reduced DNA

fragmentation and apoptotic pathways with increased Bcl-2 as the main regulator of the mitochondrial pathway for apoptosis in alveolar epithelial cells (48).

In pulmonary idiopathic fibrosis, PBM attenuates airway remodeling by adjusting pro-inflammatory and anti-inflammatory cytokines in lung tissue and inhibiting fibroblast secretion of the pro-fibrotic cytokines (34). In COVID-19 patients, IL-1β as the major cytokine in inflammatory processes increases neutrophil survival and exacerbates inflammation. PBM can reduce the severity of ARDS by lowering IL-1β levels. IL-6, as a pleiotropic cytokine plays a major role in the pathophysiological symptoms of ARDS (49). Studies have shown that PBM reduces IL-6 levels in the lungs and plasma in ARDS patients (49). Increased IL-8 in the serum of patients with ARDS contributes to neutrophil chemotaxis and survival in the lung. PBM can significantly reduce IL-8 levels in the lungs, reduce ARDS, and reduce mortality.

TNF-α causes adhesion and activation of neutrophils. It also stimulates increased IL-6 release. TNF-α levels are usually high in the lungs of COVID-19 patients. PBM is useful in reducing TNF-α levels. MCP-1 plays a crucial role in the uptake of monocytes and increases the level of monocytes in pulmonary inflammation (37). PBM can reduce monocyte migration in pulmonary inflammation by reducing MCP-1 leading to treatment (50) According to the pathophysiology of COVID-19 and PBM's potential effects on the immune system, this treatment can be effective in severe cases of COVID-19 patients with ARDS.

Radiation Exposure

Direct Radiation of PBM as LLLT on lung tissue

In PBM therapy, as a non-invasive technique that is recommended as a possible way for the treatment of COVID-19 patients, the laser is radiated directly on the lung tissue from the chest and back area. This method is called transthoracic PBM treatment which uses 810 or 940-970 nm infrared lasers that have high penetrating power in different tissues (51). In the treatment of COVID-19 patients with transthoracic PBM, the light can be irradiated into the target tissue through the skin of the chest. Studies on intracranial radiation have shown that transthoracic PBM can penetrate through the scalp and skull and reach the brain (52). These lung therapies are effective not only in treating ARDS but also in treating other diseases such as flu and pneumonia. PBM treatment is recommended due to the minimal absorption of the laser by the target tissue and the use of infrared laser in the treatment of coronavirus patients. PBM therapy helps achieve deeper penetration of the laser light into the lung tissues. As a novel approach, PBM therapy has been shown to reduce inflammation. The absence of long-term toxicity and minimal damage to other organs are among the potential benefits of this method (53).

Intravenous radiation of PBM

This technique was first used in 1970 in Russia (54). In this method, the optical fiber is inserted into a vein by a catheter (54, 55). Laser radiation can have systemic processes such as anti-inflammatory effects, modulation of the immune system, and accelerated wound healing by affecting blood cells and the immune system. This approach increases the oxygenation of the red blood cells which indirectly decreases the inflammation and repairs the damaged tissues. This approach can be carried out transcutaneous over the superficial arteries or intravenously (56). Stimulation of PBM on the blood vessels under the tongue, nasal mucosa, and other blood vessel tissues can be done by irradiation with laser or LEDs. In addition, this method of PBM therapy has regulatory effects on endothelial cell function due to its antioxidant and angiogenic effects (57).

On the other hand, lasers with different wavelengths can exert different effects. For example, green light can be used to improve oxygenation, blue light can be used to kill viruses and increase NO, and red light can be used to increase ATP (58). It can also improve blood biomarkers, increase red blood cell oxygenation, and even have beneficial effects on cellular and humoral immunity. It has been shown that laser parameters (wavelength, energy

density, etc.) play an important role in therapeutic effects (59). Studies have also shown that PBM can reduce the production of ROS in blood neutrophils. PBMs boost the immune system by increasing the number of lymphocytes and killer cells involved in defending against virus pathogens (60, 61). In another study, the effect of PBM on a female ARDS patient was investigated. According to the results of the articles, following the reduction of viral infection in the lungs, the patients were treated (62, 63).

Photodynamic Therapy (PDT)

PDT could be a novel technique for various cancerous complications induced by viruses. It also can reduce the viral load (64, 65). In recent literature, researchers found a replacement vision for viral inactivation using the PDT approach (66). PDT uses a non-toxic chemical compound termed photosensitizer (PS) that may react with dioxygen (O_2, the atmospheric oxygen), producing ROS like singlet oxygen (102) and/or anion, hydroxyl radicals, and oxide (65, 67). Most PSs belong to the groups of thiophene and polystyrene, furyl compounds, and alkaloids. These compounds have very strong phototoxic activity against virus-containing membranes. These anti-pathogenic activities are due to the chemical structures of those compounds, which ultimately prevent the virus from replicating and inactivating methylene blue (MB) and Radachlorin, which are categorized as PSs.

Typically, the antiviral effect is related to the interaction of PSs with viral or cellular molecules (68). In general, PDT is performed in three stages: stimulation of PS, formation of ROS, and damage against pathogens. The method of PDT begins with the irradiation of sunshine with an acceptable wavelength and its absorption by PS which immediately enters the three stable states of PS. The most important goals of PDT performance are the external structures of pathogens like cell walls, cell membranes, capsids, and viral coatings. Due to this, there is no need for PS to enter the microorganism (69).

PDT is one of the non-invasive treatments to eliminate viral infections and pathogens (70). Due to the spread of COVID-19, researchers are trying to suggest new efficient therapies to prevent and cure this disease (71). The molecular structure and charge of microbial pathogens are crucial for the efficacy of PDT because PS usually contains a charge.

The guanine nucleotide is a main target of ROS to inhibit viral replication. The activated PS could easily target cysteine, L-histidine, tyrosine, methionine, and tryptophan to alter their associated protein structure and functions. The hydroxyl group and singlet oxygen radical react differently to their targets. The singlet oxygen reacts more efficiently on viruses than other radicals and effectively targets guanine residues and tyrosine; histidine and tryptophan. It had been speculated that through ROS and singlet oxygen, PDT might target guanine residue and cysteine, L-histidine, tyrosine, methionine, and tryptophan to destroy the SARS-CoV-2 virus and limit the spread of COVID-19 (72).

Recent studies show that PS, such as methylene blue and riboflavin, inactivate coronaviruses. Some PS might be effective at destroying the SARS-CoV-2 virus by combining different wavelengths of light including blue, ultraviolet, and violet with several PSs such as vitamin B2, chlorophyll derivatives, and curcumin. An intravenous approach with blue light might be efficient using green-based PS such as indocyanine.

It was speculated that a combination of PDT and PBM might achieve better results in the treatment of COVID-19. During the pathogenic process of COVID-19, the receptor angiotensin-converting enzyme 2 (ACE-2) in nasal and oropharyngeal epithelial cells is the main target for virus infection. Damages to these cells with virus infection cause pneumonia and inflammation signs in patients and lead to cascades of inflammation cytokine and dysfunction of multiple organs, as well as death. PDT can be carried out using a catheter to deliver light or nebulization of PS into the respiratory tract, inactivate viruses, and reduce viral load in nasal and oropharyngeal epithelial cell membranes.

Researchers are attempting to report an efficient PDT protocol for the treatment of COVID-19 (73). In addition,

an RNA virus is also more sensitive to PDT inactivation. PDT has been used in clinics for many diseases, but there is limited information on therapeutic efficacy in COVID-19 patients. To get more accurate results, PDT therapy should be considered at different stages of COVID-19 cases. Accordingly, different types of PSs have a variety of targets and outcomes, the most important of which are the PSs that are effective in the inactivation of coronavirus pathogens. A combination of PDT and PBM therapy with various types of PSs might be an effective therapeutic strategy.

Ultraviolet therapy

UV-based therapies which include UVB and psoralen & ultraviolet A rays (PUVA), are well-known uniforms. These are highly effective treatment options for various chronic dermatoses such as cutaneous T-cell lymphomas, graft versus host disease, psoriasis, and vitiligo (74). UV radiation covers three solar spectrum ranges: UVA (320 to 400 nm), UVB (290 to 320 nm), and UVC (200 to 290 nm). (75). In addition, it is well known that UVC radiation, with an intensity of 3.75 mW/cm^2 for 60 seconds, is capable of inactivating the SARS-CoV-2 virus and preventing viral RNA transcription, translation, and replication (76).

The COVID-19 virus can affect alterations of the hematopoietic system and hemostasis and cause an accumulation of iron ions in the bloodstream (74). ORF8 and other surface glycoproteins in COVID-19 can bind to porphyrin and inhibit heme metabolism (77). In exposure to UV radiation, absorption of photons increases the stability of the iron ion bond with the pyrrolic ring of the hemoglobin molecule which prevents the heme from losing its oxygen transport function (78).

Vitamin D is a product of irradiation of UV light on the skin. Evidence shows vitamin D can affect the inhibition of IL-1, IL-6, IL-17, TNF-α, and IF-γ production leading to anti-inflammatory potential in cells (79). Also, vitamin D can modulate IL-6 which is reported to be increased in COVID-19 infections (80).

Both UVA and UVB radiation suppress hypersensitivity to viral, bacterial, and fungal antigens in patients (81). UV light has immunosuppressive effects in minimal erythema doses. Recent studies on COVID-19 patients show that UV stimulation leads to activating a cytokine cascade including prostaglandin 2, IL-4, and IL-10, that is associated with suppression of IF-γ production and reduced cytokine storm (78, 82).

Air purification as a prevention strategy

The spread of COVID-19 occurs via airborne particles and droplets. People with COVID-19 infection could spread particles and droplets of respiratory fluids that contain coronavirus through breathing, sneezing, coughing, and exhaling into the air and making bioaerosols (83). Aerosols are a suspension of particles formed by solid particles or liquid droplets dispersed and suspended in the air and bioaerosol refers to airborne particles that originate from biological sources. Viruses, spores, or biological cell debris can be considered as bioaerosols (84).

Airborne COVID-19 pandemics led to the suggestion of air purification as a prevention method for disinfecting airborne microorganisms to decrease the prevalence of COVID-19 (85, 86).

From the base study of Environmental Protection Agency (EPA) researchers about indoor and outdoor air pollution, reports that indoor air have high pollution and risk of infection because infectious droplets are exhaled outward from the patient. These droplets carry the infective virus; the droplets will spread through the air in the room or space and can accumulate. On the other hand, most people spend an amount of their time in indoor spaces which increases the risk of exposure to COVID-19 (85).

Using high-efficiency particulate air filters (HEPA), Bio-Guard filters, and air ionization is an efficient strategy for overcoming indoor air pollution but none of these systems are 100% effective (87).

Photocatalysis for air treatment is a promising technology that requires titanium dioxide (TiO2) and

visible or near an ultraviolet light source to decrease any type of pollution, especially viruses, in air streams (88). In the antimicrobial photocatalysis process, ROS is generated by irradiation to the semiconductor (SC) nanoparticle. Artificial UV light (254-365nm) is a common light source that is used in this technique. In other words, in this process of photocatalysis, SC is irradiated with compatible wavelengths as a photocatalytic material (89).

CONCLUSION

As we presented in this review, the potential positive effects of light-based therapy such as PBM, PDT, and UV therapy in balancing the function of the immune system. This treatment modality could be effective in severe COVID-19 cases with ARDS. Light-based therapy is mainly local with no delayed body response to virus elimination and has very limited adverse side effects. Considering the pathophysiology of COVID-19, light-based therapy might save the lives of severely affected patients.

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