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Cytokine 137 (2021) 155312

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Review article

Probable positive effects of the photobiomodulation as an adjunctive treatment in COVID-19: A systematic review

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ARTICLE INFO

Keywords:
Photobiomodulation
COVID-19
SARS Cov2
Low-level laser therapy
Virus
Laser therapy

ABSTRACT

Background: COVID-19, as a newly-emerged viral infection has now spread all over the world after originating in Wuhan, China. Pneumonia is the hallmark of the disease, with dyspnea in half of the patients and acute respiratory distress syndrome (ARDS) in up to one –third of the cases. Pulmonary edema, neutrophilic infiltration, and inflammatory cytokine release are the pathologic signs of this disease. The anti-inflammatory effect of the photobiomodulation (PBM) has been confirmed in many previous studies. Therefore, this review study was conducted to evaluate the direct effect of PBM on the acute lung inflammation or ARDS and also accelerating the regeneration of the damaged tissues. The indirect effects of PBM on modulation of the immune system, increasing the blood flow and oxygenation in other tissues were also considered.

Methodology: The databases of PubMed, Cochrane library, and Google Scholar were searched to find the relevant studies. Keywords included the PBM and related terms, lung inflammation, and COVID-19 -related signs. Studies were categorized with respect to the target tissue, laser parameters, and their results.

Results: Seventeen related papers were included in this review. All of them were in animal models. They showed that the PBM could significantly decrease the pulmonary edema, neutrophil influx, and generation of pro-inflammatory cytokines (tumor necrosis factor-α (TNF-α), interleukin 1 beta (IL-1β), interleukin 6 (IL-6), intracellular adhesion molecule (ICAM), reactive oxygen species (ROS), isoform of nitric oxide synthase (iNOS), and macrophage inflammatory protein 2 (MIP-2)).

Conclusion: Our findings revealed that the PBM could be helpful in reducing the lung inflammation and promoting the regeneration of the damaged tissue. PBM can increase the oxygenation indirectly in order to rehabilitate the affected organs. Thus, the infra-red lasers or light-emitting diodes (LEDs) are recommended in this regard.

1. Introduction

Coronaviridae is a family of the enveloped RNA viruses, which can infect the humans or other mammals. The two beta corona viruses known as SARS CoV and MERS CoV are among some of the well-known viruses within this family. In the recent decades, two epidemics of the acute respiratory syndrome (ARS) including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) have occurred. Mild to severe pneumonia was the main feature of these syndromes. Beginning in December 2019, a novel type of coronavirus was emerged in Wuhan, China that caused a disease known as corona virus disease 2019 (COVID-19) [1]. High transmissibility is the hallmark of this virus. The rapid worldwide distribution of the COVID-19 led to the declaration of a pandemic by the world health organization (WHO).

Epidemiologic data have shown that the median age of the patients is between 49 and 57 years old [2]. High fever, myalgia, dry cough, and dyspnea are the most common clinical symptoms of the disease [3]. Pneumonia is the hallmark of this infection. It can be distinguished from other probable types of pneumonia by the “crazy paving” lesions

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https://doi.org/10.1016/j.cyto.2020.155312
Received 4 July 2020; Received in revised form 17 August 2020; Accepted 21 September 2020
Available online 12 October 2020
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observed in the chest CT scans. They are the bilateral ground glass opacities in the parenchyma of the lungs [2]. Diarrhea, sputum production, headache, haemoptysis, rhinorrhea, sneezing and sore throat are other common symptoms of this disease [1,3]. Clinical data have suggested that the pneumonia could cause dyspnea in roughly half of the patients (Liu, 2019). One -third of the patients may develop the acute respiratory distress syndrome (ARDS) and require admission to an intensive care unit (ICU). Invasive mechanical ventilation is needed in 17 and 4% of the patients who are candidates for the extracorporeal membrane oxygenation (ECMO). Older or smoker patients are more likely to require the invasive life support [2]. Lower blood oxygenation and tissue hypoxia can be expected following the damage to the respiratory system. Concomitant tissue hypoxia can lead to a subsequent damage to the heart or central nervous system, considering their sensitivity to the blood oxygen supply.

The paraclinical findings include the hypoalbuminemia, leukopenia, lymphopenia, and low platelet counts. Increased serum level of C-reactive protein, aminotransferase [2], and lactate dehydrogenase (LDH) can be seen in these patients. The number of cluster of differentiation 8(CD8) cells may be reduced during the course of the disease [3]. Levels of some inflammatory cytokines, such as IL-1B, IL-6, interferon-gamma (IFNγ), interferon-gamma-inducible protein-10 (IP10) and monocyte chemotactic protein-1 (MCP1) increase in the serum. These cytokines increase the number and function of T helper type 1 (Th1) lymphocytes. Meanwhile, activation of T helper type 2 (Th2) lymphocytes following the release of interleukin 4(IL-4) and interleukin 10(IL-10) could also be expected. In the patients with severe disease admitted to the ICU, high levels of granulocyte colony-stimulating factor (GCSF), IP10, MCP1, macrophage inflammatory protein 1 A (MIP1A), and TNFα have been commonly found [1]. In a recent study, it was suggested to consider a "cytokine storm" in the COVID-19. Cytokine storm results in an influx of a lot of immune cells into the infection site, damage of the vascular barrier or capillaries, and may also lead to the multi-organ failure. An increase was observed in the level of many cytokines in the COVID-19 disease including IL-1β, interleukin 7 (IL-7), interleukin 8 (IL-8), interleukin 9 (IL-9), IL-10, fibroblast growth factor (FGF), G-CSF, granulocyte macrophage colony-stimulating factor (GM-CSF), IFN-γ, IP-10, MCP-1, MIP-1A, macrophage inflammatory protein 1B (MIP1-B), platelet-derived growth factor (PDGF), TNF-α, and vascular endothelial growth factor (VEGF). IL-1, TNF-α, and IL-6 are the most important pro-inflammatory cytokines. It was found that the IL-6 has a pivotal role in the COVID-19 disease especially it is associated with higher mortality [4].

Although, the clinical features of the COVID-19 are less severe than the SARS or MERS, it is more easily transmitted. The mortality rate of the COVID-19 is equal to 2–3%, while it is equal to 10 and 37% in the SARS and MERS, respectively. Presently, there is no gold standard treatment protocol available for the COVID-19. Supportive protocols are recommended most often. There is a considerable controversy about the beneficial effects of the antiviral medications and corticosteroids, although dexamethasone has been shown to be effective in reducing the deaths recently. The efficacy of the lopinavir plus ritonavir [5] has also been reported in treating the MERS. In the meantime, remedesivir [6,7] has been indicated to have a good antiviral effect in treatment of the SARS/MERS. Since, the corticosteroids can alleviate the inflammation and subsequent injury, they are also recommended for the severe cases in which standard supportive procedures were not adequate. However, there is no evidence stating that the steroids can reduce the mortality rate in ARDS in general [8]. Corticosteroids can prolong the virus clearance [1] and might cause immune suppression with concomitant susceptibility to the secondary infections [8–9]. Hyperglycemia, heart attack, hypertension, and gastrointestinal bleeding are some important side effects of the corticosteroids [8]. It should also be mentioned that nearly half of the COVID-19 patients have underlying systemic diseases like diabetes, hypertension, and cardiovascular diseases. Therefore, corticosteroid prescription might worsen the patient's underlying systemic disease. Another point is the existence of genetic polymorphisms, which can influence the patient' response to the corticosteroids. This issue might explain why some patients with ARDS may experience harmful outcomes after steroid administration [8].

The pandemic of COVID-19 underlines the importance of supportive protocols, which can reduce the inflammation in the severe cases. As previously mentioned, comprehensive evaluation of the patient's medical history is necessary to catalogue the underlying systemic diseases and the used medications. The situation is challenging in emergencies where there are many infected patients along with a shortage of medical services as observed in the COVID-19 pandemic. At the moment, there is no definitive treatment, so the therapeutic protocols should be confined to supportive treatments in order to alleviate the inflammation.

Photobiomodulation could be a promising novel treatment approach. In this non-invasive method, light-emitting diodes or low-level lasers are used to irradiate on the tissue in order to activate the cellular photo-acceptors. Irradiation is absorbed by the internal photo-acceptors like porphyrins, cytochrome *C* oxidase, and light -sensitive ion channels. Cytochrome *C* oxidase is unit IV of the mitochondrial respiratory chain, absorbing the red and near infrared wavelengths. This leads to higher electron transport, increased mitochondrial membrane potential and increased production of the adenosine triphosphate (ATP). Light-sensitive ion channels absorb the photons, which increases the concentration of the intracellular calcium (Ca2 +) ions. These processes activate several signaling pathways via reactive oxygen species (ROS), cyclic adenosine monophosphate (cAMP), nitric oxide (NO), and Ca^{2+} [10,11] (Fig. 1). These pathways influence the cellular processes like proliferation and differentiation, and can also influence other processes like inflammation as histamine release, prostaglandin production, or *cyclo*-oxygenase expression [10–13]. In this way, PBM can be helpful in accelerating the regeneration processes like wound healing and reducing the inflammation [10]. PBM has mainly local effects and can be irradiated just to a target organ without any side effects on the distant areas. Considering the anti-inflammatory and biostimulatory effects of the PBM, it seems to be a reasonable approach to be applied in controlling the COVID-19 symptoms especially in the cases with ARDS.

Therefore, this study was conducted to evaluate the direct effect of the PBM on the acute lung inflammation or ARDS and accelerating the regeneration of the damaged tissue. Moreover, the indirect effects of the PBM on modulation of the immune system or blood flow oxygenation within the tissues were also investigated.

2. Materials and methods

Our search was categorized based on the common COVID-19 symptoms including respiratory problems and also paraclinical changes influencing the blood cells or cytokines. The review strategy was constructed according to the preferred reporting items for systematic reviews and *meta*-analyses (PRISMA) checklist. The databases of Medline, PubMed, Cochrane library, and Google Scholar were comprehensively searched to find the relevant studies. Initially, there were no time or language limitations, in order to avoid missing any relevant papers. In the next step, the non-English papers were excluded from the study.

Search keywords included the combination of:

Medical Subject Heading (MeSH) Keywords: Low-Level Light Therapy [MeSH], PBM, Severe Acute Respiratory Syndrome Coronavirus 2 [Supplementary Concept], Viral Envelope Proteins [MeSH], SARS Virus [MeSH]), Respiratory Distress Syndrome, Adult [MeSH], Alveolar Epithelial Cells [MeSH], COVID-19 [Supplementary Concept], Hypoalbuminemia [MeSH], Lymphopenia [MeSH], C-Reactive Protein [MeSH], Blood Cells [MeSH], and neutrophils [MeSH].

Keywords: Light therapy, low -level laser, laser, phototherapy, PBM, photobiostimulation, photodynamic therapy, intravenous laser, corona virus, COVID-19, viral infection, virus, inflammation, lung inflammation, ARDS, acute respiratory distress syndrome, acute lung

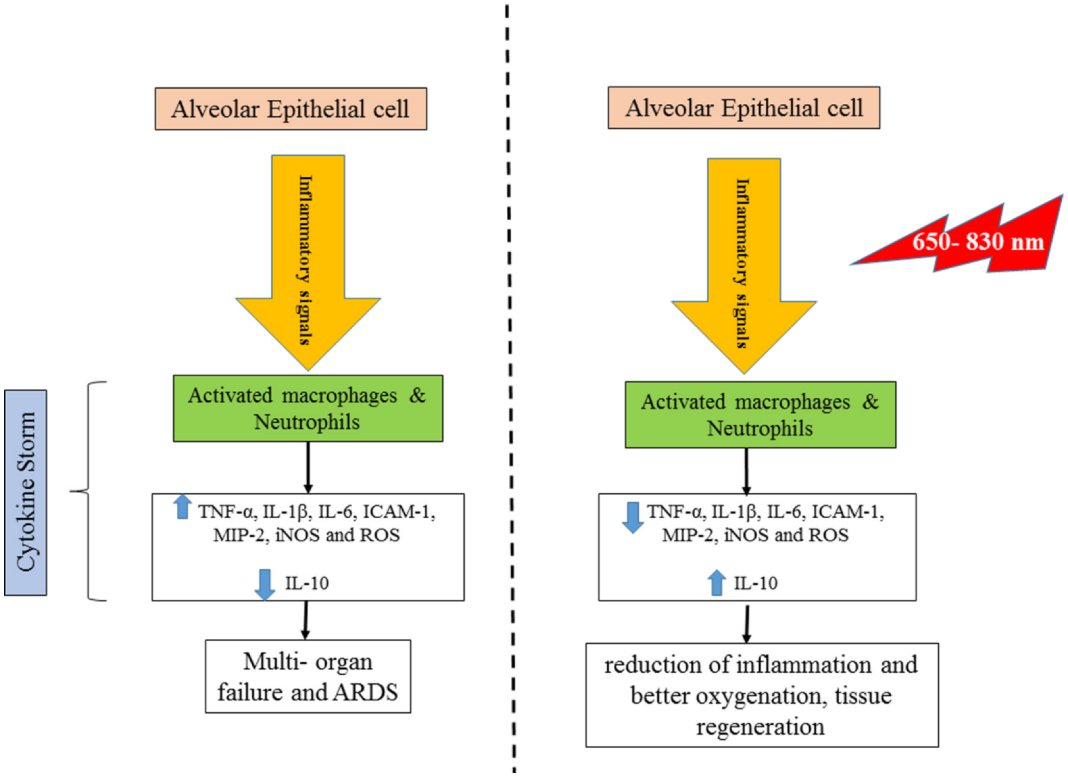

Fig. 1. Left) Cytokine storm produced by the corona virus Right) Photobiomodulation effects on the cytokines and inflammatory processes.

inflammation, SARS, MERS, alveolar epithelial cells, lung parenchyma, hypoalbuminemia, lymohopenia, C-reactive protein, lymphocyte, neutrophil, oxygenation, and lung regeneration.

The included papers were evaluated for the effect of light therapy, PBM, or low -level laser therapy on the lung inflammation, ARDS, lymphocytes, neutrophils, and lung parenchyma. Papers were categorized with respect to the type of light source, wavelength, target tissue/organ, light source parameters, and PBM results. References in all of the included papers were also reviewed.

3. Results

Totally, 161 available papers were retrieved from the PubMed database. Twelve papers were excluded due to non-English language and three papers were duplicates. There were 99 available papers on the Cochrane library and none of them were related. Search in the Google scholar database yielded 3960 papers. Fig. 1 shows the final 17 included papers in the form of a diagram. There were some related studies evaluated the effect of the PBM on the chronic respiratory inflammation (such as chronic obstructive pulmonary disease (COPD) and asthma).

Table 1 shows the related papers included in this study. All the studies confirmed that the PBM can reduce the lung inflammation, neutrophil recruitment, and pro-inflammatory cytokine production.

4. Discussion

During the clinical course of the COVID-19 disease, dyspnea can start as early as 5 days after the infection. Coughing is a major sign, indicating an inflammatory reaction in the respiratory system. Sputum production is another common sign of the disease. Ground glass opacities can be found in the chest radiographs and there are more of them in the severe cases. ARDS may occur after 8 days and it can be observed in one-third of the patients. It is a life-threatening condition, which might require invasive mechanical ventilation in 17% of the patients and extracorporeal membrane oxygenation (ECMO) in 4% of the patients. Elderly patients and smokers are more likely to require the invasive life support [2].

Although, there is no definitive treatment protocol for the COVID-19 disease yet, supportive care is the mainstay for management of the COVID-19 infection. Chloroquine, kaletra [31], remedesivir [6,7], tocilizumab, Favipiravir [31], and a combination of lopinavir and ritonavir [5] are some of the treatment options in this regard, but no definite effect has been observed on the patient's survival after treatment with these medications [31].

Corticosteroids are the most common anti-inflammatory option. Inhibiting the edema formation, leukocyte extravasation, fibrin deposition, capillary dilation, and phagocytosis are some of positive effects of the corticosteroids. Reduction of inflammation can also be induced by triggering the apoptosis of the eosinophils and lymphocytes [8,32]. It should be considered that prescription of the corticosteroids should be confined to the ICU-admitted cases with ARDS [8]. They may lead to higher susceptibility to the secondary infections [8,9] and delay the viral clearance [1].

Chan et al., suggested that the corticosteroids should only be used in the severe ARDS cases where standard supportive measures are insufficient. Corticosteroids should not be prescribed when there is a remaining infection [8]. Also, genetic polymorphisms play a pivotal role in the patient's response to the corticosteroids. A wide range of adverse reactions make the use of corticosteroids questionable in the ARDS induced by the COVID-19. Other potential side effects of the corticosteroids may affect other organs especially the liver and kidneys as major organs for metabolism. Other side effects include the hyperglycemia, polyneuropathy in the patients staying in the ICU for a long time, higher risk of necrotizing myopathy, risk of secondary infections, delayed wound healing, suppression of calcium absorption leading to the osteoporosis and avascular necrosis of the hip, and gastrointestinal ulcers [8]. Also, the corticosteroids may have negative interactions with other medications taken by the patients. This situation is more noticeable in the COVID-19 patients where nearly half of them are older and usually have underlying systemic diseases like diabetes,

Table 1
Papers included in the review.

No	Author	Year	Induction of lung inflammation	Target tissue/ organ	Light source	Light parameters	Energy density (J/cm^2)	Power density (mW/cm^2)	Evaluation method	Results
1	Aimbire et al., [14]	2005	Airway and lung inflammation induced by the Gram negative bacterial lipopolysaccharide (LPS) through intravenous injection	Rat's lung	Ga–Al–As diode laser	685 nm,12 mW, irradiation time = 1 min 20 s, spot size = 0.08 cm^2, Continuous wave	2.5	–	Rat's trachea hyperreactivity (RTHR) Bronchoalveolar lavage (BAL) lung neutrophil influx	↓ RTHR, ↓BAL ↓Lung neutrophils influx Anti- inflammatory effect was associated with inhibiting the COX-2-derived metabolites
2	Aimbire et al., (15)	2006	Immune complex formation by instillation of the ovalbumin intrabronchially followed by IV injection	Rat's lung	Ga- -Al-As laser	650 nm, 42 sec at 5 min after induction, continuous mode, 0.04, 0.11, and 0.22 Joules Spot size = 0.08 cm^2 Irradiated through the skin over upper bronchus	–	12.5, 31.25, and 62.5	Bronchoalveolar lavage (BAL) TNF-α level by Cytotoxicity assay through the use of L-929 tumor cells	↓↓TNF-α expression LLLT reduced the TNF-α level in a dose- dependent manner. The irradiation energy of 0.11 J had the best efficacy.
3	Aimbire et al.,(16)	2008	Acute lung injury induced by IV injection of lipopolysaccharide (LPS) (5 mg/kg)	Rat's lung	Diode laser	660 nm, 30 mW spot size = 0.785 cm^2 skin over the upper bronchus	7.5	–	Lung permeability via assessing extravasated albumin concentration in the lung homogenate Inflammatory cell (neutrophil) influx by myeloperoxidase (MPO) activity IL-1β in BAL by the enzyme-linked immunosorbent assay (ELISA) IL-1β mRNA expression in the trachea by the real time polymerase chain reaction (RT-PCR)	↓Lung permeability ↓ Neutrophils influx ↓ MPO activity ↓ IL-1β expression and its mRNA Laser showed an anti-inflammatory effect at 4, 12 and 24 h after LPS exposure.
4	Mafra de Lima et al., (17)	2009	TNF-a-induced acute lung inflammation	Rat's dissected bronchi with or without TNF-α	Ga- Al-As laser	650 nm, 2.5 mW, spot size = 0.08 cm^2, 0.44 J, irradiation time = 42 s	1.3 J/cm^2 in two sessions (total dose = 2.6 J/cm^2)	31.25	Evaluation of the bronchi smooth muscles (BSM) by response to Acetylcholine and Isoproterenol cAMP concentration TNF-α mRNA expression in the BSM tissue by the RT-PCR	PBM reduced the BSM hyperreactivity or relaxation after Acetylcholine and Isoproterenol application, respectively. ↓TNF-α mRNA expression
5	Mafra de Lima et al., (18)	2010	Acute pulmonary inflammation induced by aerosol lipopolysaccharide from *Escherichia coli* (0.3 mg/ mL)	Rat's lung	Ga- -Al-As diode laser	650 nm, 2.5 mW, spot size = 0.08 cm^2, irradiation time = 42 s skin over the upper bronchus	1.3	31.2	Neutrophil recruitment and activation evaluated by edema. BAL fluid cellularity and MPO activity. mRNA expression of TNF-α, IL-1β, IL-10, cytokine -induced neutrophil chemoattractant-1 (CINC-1), MIP-2 and ICAM-1 by the RT-PCR Proteins levels by the ELISA	↓ Pulmonary edema ↓ Neutrophil influx ↓ Endothelial cytoskeleton damage ↓TNF-α expression ↓IL-1β expression ↓ICAM-1 expression. Levels of CINC-1, MIP-2, and IL-10 were not influenced by the laser irradiation.
6	Mafra de Lima et al., (19)	2010	4 h incubation with LPS or H2O2 for inducing the acute lung inflammation	Rat's AM cell line AMJ2-C11	Diode laser	660 nm, 30 mW, spot size = 0.785 cm^2, irradiation time = 252 s	4.5		MIP-2 mRNA expression by the RT-PCR Intracellular ROS generation by 2′,7″ dichlorofluorescin diacetate (DCFH-DA) NF-kB protein by the ELISA	↓MIP-2 mRNA expression ↓ Intracellular ROS generation
7		2011		Rat's lung	Diode laser		6.9	38.4		

(*continued on next page*)

Table 1 (*continued*)

No	Author	Year	Induction of lung inflammation	Target tissue/ organ	Light source	Light parameters	Energy density (J/cm^2)	Power density (mW/cm^2)	Evaluation method	Results
	Mafra de Lima et al., (20)		Acute lung inflammation induced by the intestinal ischemia and reperfusion			660 nm, 30 mW, 5.4 J, spot size = 0.08 cm^2 Irradiation time = 3 min skin over the upper bronchus			Lung edema by Evans blue extravasation Pulmonary neutrophils influx by the MPO activity TNF and IL-10 expression in the lung by the RT-PCR TNF and IL-10 protein in the lung by the ELISA	↓Lung edema ↓Neutrophils influx ↓MPO activity ↓TNF expression and production ↑ IL-10 production
8	Mafra de Lima et al., (21)	2011	Acute lung inflammation induced by the LPS inhalation or TNF intra nasal instillation	Rat's dissected bronchi	InGaAlP laser	660 (685) nm, 8.82 J, irradiation time = 252 s On the skin over the right upper bronchus	4.5	17.85	TNF mRNA expression by the RT- PCR and protein levels by the ELISA cAMP levels by the ELISA	PBM increased the cAMP level indirectly in the alveolar macrophages by a TNF-dependent mechanism.
9	Mafra de Lima et al., (22)	2013	Acute lung injury induced by the gut ischemia and reperfusion	Rat's lung	Diode laser	660 nm, 30 mW, 5.4 J, continuous mode, irradiation = 180 s, spot size = 0.08 cm^2 skin over the bronchus in direction of the trachea distal two series of laser irradiation: a) 5 min after initial or 5 min before the end of the intestinal reperfusion b)30 min after the beginning of the reperfusion	6.9	38.4	Lung edema by Evans blue extravasation Bronchoalveolar lavage fluid neutrophils by the MPO activity Injury score by the lung histology ROS generation by fluorescence ICAM-1 and PPARy expression by the RT-PCR Lung HSP70 and glutathione (GSH) protein by the ELISA Brown stain for immunohistochemical localization of the ICAM-1	↓Lung edema ↓Neutrophils influx ↓MPO activity ↓ ICAM-1 mRNA expression ↓ROS formation ↑GSH concentration in the lung ↑HSP70 expression ↑peroxisome proliferator-activated receptor y (PPARy) expression PBM reduced the acute lung injury induced by the gut ischemia and reperfusion.
10	Mafra de Lima et al., (23)	2013	ARDS induced by the intestinal ischemia and reperfusion	Rat's lung	Diode laser	660 nm, 30 mW, 5.4 J, continuous mode, irradiation = 3 min spot size = 0.08 cm^2 skin over the upper bronchus	7.5	31.25	Lung edema by Evans blue extravasation Pulmonary neutrophils influx by the MPO activity mRNA expression of the TNF-α, IL-10, ICAM-1, and isoform of NO synthase (iNOS) by the RT-PCR TNF-α, IL-10, and iNOS proteins in the lung by the ELISA	↓ Airway reactivity dysfunction by:↓lung edema ↓MPO activity ↓ TNF-α expression ↓ iNOS expression ↓ ICAM-1 expression ↑ IL-10.
11	Mafra de Lima et al., (24)	2014	ARDS induced by the intestinal ischemia and reperfusion	Rat's lung	Diode laser	660 nm, 30 mW, 5.4 J, continuous mode, irradiation = 5 min spot size = 0.08 cm^2 skin over the upper bronchus	1, 3, 5 and 7,5	–	Neutrophils influx by the MPO activity mRNA expression and protein concentration of the IL-1β, IL-6, IL-10, and TNF by the RT-PCR and ELISA, respectively	↓↓IL-6 mRNA expression ↓↓ TNF mRNA expression However, IL-1β and MPO activity were reduced by all doses except 1 J/cm^2. PBM increased the IL-10 protein in the irradiation energy of 1 J/cm^2.
12	Oliveira et al., (25)	2014	Acute lung inflammation and ARDS induced by the LPS	Rat's lung	Infra-red laser	830 nm, 35 mW, 80 s per point, 3 points per application (total 240 s), continuous mode Direct contact to skin point 1 was in the end part of trachea, points 2 and 3 were in the right and left lungs respectively	9	–	Differential cell count in the BAL Levels of cytokines (IL-1beta, IL-6, KC, and TNF-alpha) in the BAL fluid	PBM significantly reduced the inflammation in the LPS-induced ARDS. ↓Number of total cells ↓Neutrophils in BAL or lung parenchyma Levels in BAL fluid and in serum of: ↓ IL-1beta ↓IL-6 ↓ KC ↓TNF-α.

(*continued on next page*)

Table 1 (*continued*)

No	Author	Year	Induction of lung inflammation	Target tissue/ organ	Light source	Light parameters	Energy density (J/cm^2)	Power density (mW/cm^2)	Evaluation method	Results
13	Miranda da Silva et al., (26)	2015	Lung inflammation induced by the formaldehyde (1%) or vehicle inhalation (distillated water)	Rat's lung	Diode laser	660 nm, 30 mW, spot size = 0.14 cm^2, 60 s/point, 1.8 J for 1 min	12.86	210	Blood cell count MPO activity for neutrophil influx Evans blue for lung vascular permeability ELISA for the level of IL-6, TNF-α, and IL-10 in the BAL RT-PCR assay for IL-6, IL-10, and HPRT for gene expression Histology for lung morphological changes	↓Neutrophil influx (MPO activity) ↓ Leukocyte number ↓ Degranulation of the mast cells ↓ Lung Microvascular permeability. ↓IL-6 ↓ TNF-α ↑ IL-10 generation
14	Oliveira et al., (27)	2015	ARDS induced by the LPS intratracheally or intraperitoneally	Rat's lung	Infra-red laser	830 nm, 35mW, 80 s per point 3 points per application) direct contact with the skin	3		Total and differential cell counts in the BAL Levels of cytokines (IL-1beta, IL-6, KC, and TNF-alpha) in the BAL and serum Neutrophils count in the lung parenchyma	PBM significantly reduced the ARDS in both inducing ways. ↓Total cells and neutrophils count in the BAL ↓ Neutrophil count in the lung parenchyma, Levels in the BAL and in serum of: ↓ IL-1beta ↓ IL-6, KC ↓TNF-α IL-10 level was not increased by the PBM.
15	da Silva Sergio et al.,(28)	2018	Acute lung injury induced by the intraperitoneal injection of LPS from Escherichia coli	Alveolar epithelial cells of the rat's lung	-Ga-Al-As diode laser	808 nm, 100mW, Spot size = 0.028 cm^2, 2 and 5 J energy per point, four points of irradiation, time = 2 and 5 s per point Skin over the lung	10 20	3.571	caspase 3 and Bcl-2 mRNA levels by the RT-qPCR DNA fragmentation by the TUNEL (terminal deoxynucleotidyl transferase-mediated 2′-deoxyuridine, 5′-triphosphate nick-end-labeling) assay	↑ Bcl-2 mRNA levels ↓ caspase-3 mRNA levels DNA fragmentation: ↓ in the alveolar cells but ↑ in polymorphonuclear cells, which induced the apoptosis in these inflammatory cells.
Indirect PBM										
16	Fujimaki et al.,(29)	2003	Isolated neutrophils from the human's peripheral blood samples	Human blood	Ga-Al-As laser	830-nm continuous wave, 1000 mW, spot size 6.6 cm^2, irradiation time = 30 or 60 sec	9.5 19.0 J/cm^2	150 mW/ cm^2	Production of ROS by luminol-dependent chemiluminescence (LmCL) expression of CD11b and CD16 neutrophil surface by the flow cytometry	PBM attenuated the ROS production in the neutrophils and reduced the oxidative tissue injury.
17	Al Musawi et al.,(30)	2016	Human's whole blood sample	Human blood	Diode laser	Wavelengths of 405, 589, and 780 nm, 10 mW, spot size = 0.332 cm^2, irradiation time = 20, 30, 40, and 50 min	36, 54, 72, and 90	30	Lymphocyte count Flow cytometry	Photobiomodulatory effects were related to the laser parameter. Wavelength of 589 nm and fluence of 72 J/cm^2 resulted in the best results. ↑↑ CD45 lymphocytes and natural killer (NK) (CD16, CD56) cells There was no significant change for CD3 T lymphocytes, T-suppressor (CD3, CD8) cells, T-helper (CD3, CD4) cells, and CD19 B lymphocytes

↓ shows the reduction in the target variable. ↓↓ shows a significant reduction in the target variable. ↑ shows an increase in the target variable.↑↑ shows a significant increase in the target variable.

hypertension, cardiovascular diseases, etc., requiring the additional medications or have compromised immune systems. Moreover, COVID-19 sharply lowers the blood oxygenation, which can directly damage the pulmonary tissues or indirectly damage the other organs like the heart or brain by inducing the hypoxia.

Our experience in the recent COVID-19 pandemic suggests that the clinicians should consider a comprehensive evaluation of the patient's medical condition, medications, systemic diseases, genetic polymorphisms that may affect the drug reactions. These factors make it complex for the clinicians to manage an emergency like the COVID-19, involving large numbers of the infected people along with insufficient medical services. As mentioned above, there is not yet any definite treatment for the COVID-19 therefore, every possible intervention, which may help to reduce the inflammation and restore the respiratory system or other impaired tissues could be tried for managing the COVID-19 progression. This could be achieved by direct rehabilitation of the damaged tissue, or indirectly by increasing the oxygenation and blood flow. So, reducing the inflammation and aiding the tissue regeneration are the major goals of the clinicians. It is important for the clinicians to choose the treatment modalities with the least drug interactions or side effects.

Photobiomodulation is an innovative approach in this regard. It is a non-invasive approach in which the LEDs or low -level lasers are used to produce the red or near- infrared (NIR) light absorbed by the cellular photo-acceptors. This light absorption produces the ROS, such as singlet oxygen, hydrogen peroxide (H_2O_2), and superoxide [33–35]. These ROS affect many cellular processes, such as proliferation, differentiation [12,13,36–38], adenosine triphosphate (ATP) formation [39,40] and also can reduce the inflammtion [10]. So, PBM is a helpful approach when the cellular function is impaired especially by the hypoxia [41]. Previous studies have shown the advantages of the PBM including anti-inflammatory effects and acceleration of the wound healing [10]. These features operate alongside the general effects of the PBM for balancing the metabolic, analgesic, and immunomodulatory conditions. One advantage of this approach is that it is applied locally without any systemic side effects on the other organs [31]. Based on the aforementioned advantages of the PBM and the current lack of established treatments for COVID-19 disease, it seems that the PBM could be helpful in controlling the COVID-19 disease as an alternative or adjunctive treatment, particularly in the severe cases with ARDS.

Table 1 shows the related papers used the PBM for treatment of lung inflammation or ARDS. The majority of studies have used the red diode lasers (650 and 660 nm) with an energy density within the range of 1–12.86 J/cm^2 and power density within the range of 12.5–210 mW/cm^2. Three papers [25,27,28] have used the infra-red lasers (808 and 830 nm) with an energy density within the range of 3–20 J/cm^2 and there was not sufficient information about the power density except in one paper (3.571 mW/cm^2 [28]. All the papers have shown the anti-inflammatory effects of the PBM including reducing the lung edema, cytokines in the bronchoalveolar lavage (BAL) fluid, neutrophil influx, myeloperoxidase (MPO) activity, and damage to the endothelial cytoskeleton.

The mechanisms of action of the PBM involve many factors related to the inflammation such as:

1- Activating the interferons (IFNs) having a pivotal role in the defense against viruses and the modulation of the immune system. Huang et al., [1] found a higher level of IFN-γ in the COVID-19 patients. IFN-γ has antiviral and anti-tumor activity, and also increases the T lymphocytes and natural killer cells. It can regulate the immune system reactions. IFN-α and IFN-β stimulate the natural killer cells and macrophages, they can also stimulate the lymphocytes and macrophages in order to improve the antiviral or anti-tumor activity [42–44].
2- PBM can also activate the phagocytes engulfing and removing the microorganisms (like bacteria or viruses) as well as apoptotic cells [27,45].
3- PBM can increase the micro and macro-circulation in order to increase the tissue or organ resistance against the external harmful factors [46].
4- It also can increase the oxygen saturation of the tissues, which in turn increases the cell metabolism and capacity for proliferation or regeneration of the damaged tissue [47].

Based on Table 1, there are several cytokines influenced by the PBM.

1- TNF-α

According to the literature, PBM can reduce the expression of TNF-α mRNA and its production levels [15,17,18,20,21,23–27]. Neutrophil adhesion and activation can be influenced by the TNF-α and also IL-6 generation can be stimulated by the TNF-α. Moreover, TNF-α can promote the coagulation and edema in the acute lung inflammation [15,48].

2- Interleukin-1beta (IL-1β)

IL-1β, as the main inflammatory cytokine contributes to the initiation of inflammation. Neutrophils are the main source of this cytokine and it increases the survival rate of the neutrophils in a reciprocal manner. Severe cases of ARDS with poor prognosis show higher levels of IL-1β. Many studies have confirmed its effects in the acute lung inflammation. It has been found that the PBM can reduce the production of this cytokine [16,18,24,25]. Mafra de Lima et al. [24] revealed that the IL-1β expression and concentration were not reduced by the energy dose of 1 J/cm2, but on the other hand, they were reduced by higher doses (3, 5 and 7.5 J/cm2). Therefore, it is necessary to provide a sufficient energy dose to the target tissue, especially the lung parenchyma. Laser irradiation will be attenuated by the passage through overlying tissue, such as intercostal muscles and skin.

3- Interleukin-6 (IL-6)

PBM can reduce the IL-6 levels during the acute lung inflammation or ARDS [24–27]. This cytokine prolongs the duration of inflammation [49–50] and is related to the poor prognosis in ARDS [49,51–53].

4- Interleukin-10 (IL-10)

Studies have shown that the low -level laser can increase the IL-10 generation. IL-10, as an anti-inflammatory cytokine can modulate the production of other inflammatory cytokine or reduce the tissue injury. It has been suggested that there is a balance between the TNF and IL-10 production [54]. So, the TNF production can be reduced by promoting the IL_10 formation by the PBM. This protective effect has been demonstrated in several studies [20,23–24,26]. It has been found that the PBM increases the IL-10 production. In contrast, two studies [18,27] have shown that the low -level laser does not influence the IL-10 production.

5- Intercellular Adhesion Molecule-1 (ICAM-1)

Neutrophil recruitment and their chemotaxis from the bloodstream to the lung parenchyma is one of the hallmarks of the acute lung inflammation or ARDS. There are some cytokine- induced neutrophil chemoattractants (CINCs) present on the neutrophils and endothelial cells. CD18 integrin is present on the polymorphonuclear leukocytes (PMNs). However, ICAM-1 is a related adhesion molecule on the endothelial cells. It has been shown that the PBM reduces the ICAM-1 expression [18,22,23]. It has been suggested that the inhibitory effect of the PBM on ICAM-1 expression may be related to the suppression of

TNF-α and IL-1β production. This may be another mechanism by which the PBM reduces the lung inflammation.

6- Macrophage Inflammatory Protein-2 (MIP-2)

MIP-2 is another neutrophil chemoattractant. It is secreted by the monocytes and neutrophils at sites of inflammation. It can attract the leukocytes and hematopoietic cells. Therefore, inhibition of MIP-2 generation by the PBM may have a pivotal role in reducing the lung edema [18–19].

7- ROS and Isoforms of NO Synthase (iNOS)

ROS can be produced by the laser irradiation of the cells. Superoxide or hydrogen peroxide (H_2O_2) are some examples in this regard [33–35]. ROS can change the cellular process as the secondary messengers at low concentrations. Nitric oxide (NO) is beneficial at low concentrations, but at high concentrations, it can react to produce the reactive nitrogen species (RNS), such as peroxynitrite. Both ROS and RNS are destructive at high doses. In the lung inflammation, the increased neutrophil influx produces high concentrations of ROS and RNS damaging the lung tissue. Some studies have shown that the PBM can reduce the ROS formation [19,22] or lower the iNOS levels [23].

There are two approaches to deliver the light used in the PBM.

4.1. Transthoracic approach

This involves a direct irradiation of the target organs [31]. In the COVID-19 disease, the lungs can be irradiated through the chest skin or through the back area when the patient is in the prone position. Studies on the transcranial irradiation have demonstrated that the light can penetrate through the scalp and skull to reach the brain [55]. As mentioned above, red and NIR wavelengths have been used in this regard. PBM should irradiate through the interchondral space so that, the laser clusters are applied over the entire surface of the thorax. Infrared wavelengths (e.g., 810 nm) are suggested for the PBM, because less laser irradiation will be absorbed by the overlying tissues. Infrared lasers have lower tissue absorption compared to the red lasers.

High-intensity laser therapy (HILT) may be helpful to achieve deeper penetration of the laser light to the underlying tissues, especially lung tissues. HILT has been shown to reduce the inflammation by a non-invasive approach [56].

The lack of any long-term toxicity, gene mutations, and damage to other organs are among the potential advantages of this approach. There has not been any bacteremia observed after irradiation, which is beneficial for the immune-suppressed patients.

4.2. Intravenous approach

This approach increases the oxygenation of the red blood cells, and influences the biomarkers in order to indirectly decrease the inflammation or regenerate the damaged tissues. This approach can be carried out intravenously, transmucosally, or transcutaneously over the superficial arteries. Blood vessels in the easily accessible areas like the nasal mucosa, under the tongue, behind the knee, or on the wrist can be irradiated with the laser or LEDs. Oxygenation can be increased by the green lasers however; viruses could be cleared by the blue laser irradiation. Red lasers improve the ATP production. [31,57] Therefore, using visible lasers is recommended in this approach with an adjusted dosage.

Two studies have supported the use of this approach [29–30]. They have shown that the laser parameters (wavelength, energy density, etc.) have a critical role in the therapeutic effects [30]. It has been shown that the PBM could reduce the ROS production in the neutrophils in peripheral blood [29], and PBM could regulate the immune system by increasing the lymphoctes and neutral killer cells involved in the defense against the viruses [30].

There was just one clinical study which successfully treated a female patient with ARDS following a secondary viral infection [58]. Clinicians used the PBM (820 nm and 50 mW) in order to reduce the lung inflammation. Laser was delivered to the skin between the ribs. This study was a case-report, so it was excluded from our study.

Other immunomodulatory effects of the PBM may be expected by irradiating the lymphoid tissues like the thymus, spleen, bone marrow, or the lymphatic system.

5. Conclusion

Despite the lack of available studies on the PBM effects on the COVID-19, but it is assumed that the PBM may be a helpful adjunctive treatment in management of the COVID-19 disease. PBM can reduce the lung edema, neutrophil influx and promote the regeneration of the lung tissue and better oxygenation for all the related organs. Infra-red lasers are recommended because of their higher ability for penetration into the lung tissue. Dosimetry of 6.5–7.5 J/cm^2 energy density is suitable for the red lasers and an amount of 9.5–10.5 J/cm^2 is a suitable dose for the infra-red lasers. Continous mode irradiation at different points of the respiratory system may be helpful in management of the COVID-19 pneumonia. PBM may be used as a preventive approach in the high -risk patients who could receive pre-treatment PBM while being still at a relatively mild stage of the disease. Also, PBM may be considered as a therapeutic approach in the hospitalized patients before their condition worsens sufficiently to require the ICU admission. Therefore, randomized clinical trials should be carried out on the PBM effects for the COVID-19 disease, and indeed some have already been started in various parts of the world.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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