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Review

Light as a Cure in COVID-19: A Challenge for Medicine

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Abstract: Light and lasers, as high-tech devices whose medical potential has yet to be fully discovered, have made important contributions to medicine, even in the current pandemic. The main aim of this review was to investigate how light was applied as a therapeutic tool during a crisis triggered by COVID-19. Another goal was to encourage scientists and industry to quickly design new at-home photobiomodulation therapy (PBMT) and/or antimicrobial photodynamic therapy (aPDT) easy to use systems to end this pandemic, especially for those who believe in high-tech but would never get vaccinated. This review revealed that PBMT has been successfully applied as adjunct therapy, in combination with conventional medical treatment, and as a pioneering action in SARS-CoV-2 infection, demonstrating significant improvements in airway inflammation and general clinical condition of patients, a faster recovery, avoiding intensive care unit (ICU) hospitalization, mechanical ventilation, mortality, and overcoming long-term sequelae. Application in only a limited number of cases strongly suggests the need for future randomized, placebo-controlled clinical trials to objectively determine the action and effects of PBMT in COVID-19. Implementation of unparalleled theragnostics methods and light-based techniques for disinfection of spaces, air, skin, mucosae, and textures to decrease the load of SARS-CoV-2 virus would save lives, time, and money. In this ongoing and challenging search for the seemingly intangible end of this pandemic, a non-invasive, easily accessible, safe, and side-effect-free adjuvant method appears to be PBMT, alone or in synergistic combination with aPDT, which has been shown to work in COVID-19 and opens unprecedented potential for use as home self-treatment to end the pandemic.

Keywords: antimicrobial; cytokine storm; hyperinflammation; immunomodulation; lasers; LEDs; photobiomodulation; photodynamic therapy; SARS-CoV-2

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1. Introduction

Originally from Wuhan, China, at the end of 2019, SARS-CoV-2 virus infection spread rapidly around the world and became a recognized ongoing pandemic with a significant overall mortality rate, leading to a global health crisis with multiple interferences and other implications. The disease has been named by the World Health Organization (WHO) as COVID-19 (CO for crown, VI for virus, D for disease, and 19 for the year it was first diagnosed) and continues to be present worldwide, even if after multiple mutations and variants, as well as the introduction of new dedicated vaccines, even though we expected extinction. Coronaviruses came up as a threat and danger to public health in the 21st century, with high morbidity and mortality rates, especially in the elderly and immunocompromised people. COVID-19 stands third as respects fatal coronavirus diseases, after SARS-CoV (severe acute respiratory syndrome coronavirus), and MERS-CoV (Middle East respiratory syndrome coronavirus). Its outbreak was declared by the WHO in January 2020 as the sixth global health emergency. One year later, 64 million people worldwide were affected by the disease, and the global economy lost more than $1 trillion. The COVID-19 pandemic has activated the greatest worldwide economic crisis in the last few centuries. In 2020, economics has contracted in 90 percent of countries, the world economy has diminished by about 3 percent, and global poverty has increased for the first time to all the people at about the same time. Governments have tried to respond quickly and comprehensively to mitigate the worst immediate economic effects of the crisis, but there are still economic frailties, and new comprehensive measures are needed to reduce the interconnected financial risks generated by the pandemic and to turn toward an upheld and fair recovery for all the world's economies. The global economy has lost nearly $8.5 trillion in production over the past two years, and the key United Nations (UN) report released in January 2022 showed that the fast transmission of the Omicron variant prevented the rapid recovery of the global economy, which was predicted by the end of 2021. As of 25 July 2022, the number of coronavirus cases worldwide was 575,357,868 [1–8].

An inadequate immune response plays a key role in the pathophysiological mechanisms and could lead to a dramatic evolution of adult patients with severe forms of COVID-19 but also of children, especially those with autoimmune diseases. The discovery of new immunoregulatory products and treatment methods could optimize their health and safety in the era of COVID [9]. Currently, there are no 100% effective antiviral drugs for preventing or treating SARS-CoV-2 infection. Immunoengineering is extensively studying new methods to improve the absorption of new oral drugs and vaccines for COVID-19 [10].

Vaccination against COVID-19, which is currently available worldwide through several types of vaccines, provides protection for some variants but not enough for subsequent waves. Vaccines were designed and tested in record time, which has generated confusion, high levels of anxiety and misperception of risks, and diverse behaviors that have sparked opposition and incredible indecision around the world. For future vaccination strategies against COVID-19 to achieve the desired results, important challenges must be overcome to gain greater confidence in vaccines and to expand their access in low-income countries [11].

PBM could be a safe and promising therapy to successfully treat COVID-19. Complementary to allopathic treatments, PBM management of SARS-CoV-2 infection as a non-pharmacological integrative therapeutic modality could prevent morbidity and mortality, accelerate recovery, and improve the quality of life of patients diagnosed with COVID-19, as new advances are in course [12].

The main aim of this review was to investigate how light was applied as a therapeutic tool during a crisis triggered by COVID-19. Another goal was to encourage scientists and industry to quickly design new at-home photobiomodulation therapy (PBMT) and/or antimicrobial photodynamic therapy (aPDT) easy kits to end this pandemic, especially for those who believe in high-tech but would never get vaccinated.

2. Photobiomodulation in COVID-19

The history of the use of light in modern medicine dates to the early 1900s, when Finsen reported significant recoveries of smallpox patients exposed to red light compared to unexposed controls [13–15].

Finsen was awarded the Nobel Prize in 1903 "in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science" [16].

The exceptional demonstrations of N.R. Finsen have inaugurated a new stage in contemporary medicine regarding the effectiveness of light therapies, followed by implementing new laser technologies after Endre Mester incidentally detected the positive effect of a ruby laser beam on hair growth and wound healing in mice [17,18].

Originally called Low Level Light/Laser Therapy (LLLT), nowadays, photobiomodulation (PBM) is a modality that consists of projecting light to influence the activity of living cells, tissues, and even the entire organism to stimulate the immune system, promote tissue repair, advance healing, decrease inflammation, and control pain.

Later, less expensive light-emitting diodes (LEDs), LED clusters, and so on were applied, low-cost devices, and more affordable for every clinic or patient.

PBM protocols were initially dictated by in vitro cell studies or performed on small animal models, so when translated to medical applications deep within the human body, the results were not as expected, and it was wrongly concluded that PBMT was not effective. Errors have been subsequently corrected by many positive, randomized double-blind, placebo-controlled studies, starting from appropriate devices and parameters, as well as correctly calculated doses to effectively reach and penetrate the target tissues. The number of carefully chosen devices, the wavelengths, and the parameters of the PBMT protocol selected effectively and properly can lead to the safe medical success of PBMT, even if there is not yet an unanimously accepted agreement on the parameters and protocols for its various clinical applications [19–22].

Since then, PBMT has been applied in many medical fields. The use of PBMT in the COVID-19 pandemic began with experience, implementation, and previous results on models of acute lung injury, lung inflammation, and acute respiratory distress syndrome (ARDS), precisely for its potency in ameliorating inflammatory processes and preserving lung function [23–25].

Sabino et al. have published a paper in which they summarized the benefits, challenges, and strategies for combating the COVID-19 pandemic using light-based technologies [26].

Photobiomodulation uses low-level (low-power) lasers, light-emitting diodes, and other light sources on cells, tissues, or the entire surface of the body to stimulate and enhance cellular functions by non-invasively activating internal cellular photoreceptors, such as porphyrins, light-sensitive ion channels, and cytochrome C oxidase (CCO), or Complex IV, which is the last enzyme in the respiratory electron transport chain located in the inner mitochondrial membrane, capable of absorbing wavelengths from red to near-infrared region. As a result, electron transport, as well as the potential of the mitochondrial membrane and the generation of adenosine triphosphate (ATP), known as the "molecular unit of currency" of intracellular energy transfer, increase [27–30].

A second assumption is that photons, after being absorbed inside the light-sensitive ion channels, will increase the concentration of intracellular calcium ions (Ca^{2+}), will stimulate the signaling pathways through Ca^{2+}, nitric oxide (NO), reactive oxygen species (ROS), and cyclic adenosine monophosphate (cAMP), having a significant impact on protein synthesis, cell migration, proliferation and differentiation, anti-inflammatory signaling, anti-apoptotic proteins, antioxidant enzymes, and the production of prostaglandins, or the expression of cyclooxygenase and thus generating a cascade of anti-inflammatory and biostimulatory effects, i.e., contributing to healing (also through stem cells and progenitor cells especially sensitive to PBM). The effects of PBM seem to be limited to a specified set of wavelengths and involve the existence of a biphasic dose response or the Arndt–Schulz curve, i.e., lower doses are often more beneficial than high doses. Research is underway on PBM mechanisms [29,31,32].

2.1. PBM Applied in Pulmonary Inflammation Caused by COVID-19

The first case report of a 57-year-old African American male with severe COVID-19, to whom PBMT was applied as adjunctive or supportive therapy to treat lung infection and prevent the cytokine storm, was published by Sigman et al. in August 2020. The authors relied on the pre-pandemic findings of scientific studies on human subjects but also on experimental models of respiratory diseases, which had already scientifically proven that PBMT is an adjuvant safe therapy with important anti-inflammatory and regenerative effects in lung disorders. PBMT was applied with a laser in scanner mode (with near-infrared wavelengths of 808 nm in pulses, and 905 nm in super-pulses), 28 min at each session, i.e., 14 min each lung, for four consecutive days, with the patient in the prone position. Both laser diodes operated synchronously and simultaneously with coincident propagation axes, as follows: (1) GaAlAs diode (808 nm), peak power: 3 W, pulse duration: 333 μs, dose: 7.2 J/cm^2; (2) GaAs diode (905 nm), peak power: 75 W × 3, pulse duration:

100 ns, dose: 113.4 mJ/cm^2. For both laser diodes, the modulation frequency was equal to 1500 Hz, the total scanned area was 25 × 10 = 250 cm^2, and the total energy delivered was 3600 J per session. An energy density of 7.2 J/cm^2 over the skin penetrated the chest wall (1.6 to 6 cm) to provide the lung with just over 0.01 J/cm^2 of laser energy, which proved to be sufficient for biostimulation. The patient tolerated all four daily sessions well and had an important amelioration in breathing right after each therapy. The subject was assessed previously and post-therapy by blood tests, radiographic assessment of lung edema (RALE), indices of pulmonary severity, oxygen demands, and a set of questions. PBMT results were good, as follows: oxygen saturation increased from 93–94% to 97–100%, oxygen demand decreased from 2–4 L/min to 1 L/min, RALE improved from 8 to 5, and the pneumonia severity index ameliorated from 142 (Class V) to 67 (Class II). Other additional pulmonary indices both declined from 4 to 0. C-reactive protein (CRP), initially equal to 15.1 mg/dL returned to normal (1.23 mg/dL), and the subject reported a substantial improvement in the perception of pneumonia in a couple of days, without necessity for artificial ventilation. In this case report, PBMT modulated the immune system, reduced inflammation and edema, and stimulated healing processes, being non-invasive, cost-effective, and without known side effects. The authors agreed on the request for further controlled clinical trials to investigate in depth the results of PBMT on the outcome of severe cases of COVID-19 [33].

Another case published by Sigman et al. refers to a 32-year-old Asian patient with morbid obesity and severe COVID-19 who received four consecutive sessions of once-daily PBMT via a dual-wavelength pulsed 808 nm laser scanner (diode GaAlAs, 3 W, frequency 1500 Hz, 330 microseconds pulse duration) and 905 nm (GaAs diode, 75 W × 3, super-pulsed 1500 Hz, 100 nanoseconds pulse duration) administered over the posterior thorax for 28 min. Each lung was scanned at a distance of 20 cm above the skin for 14 min from apex to base over a 250 cm^2 area of the posterior thorax with a dose of 7.2 J/cm^2 and a total delivered energy equal to 3600 J. Initially, the SpO_2 measured by pulse oximetry was 88–93% at 5–6 L of oxygen received, and after PBMT, SpO_2 increased to 97–99% at 1–3 L of oxygen required. At the same time, there was a decrease in the RALE score from 8 to 3, and the Brescia-COVID indices decreased from 4 to 0, and the SMART-COP decreased from 5 to 0. The level of interleukin 6 (IL-6) decreased from 45.89 to 11.7 pg/mL, ferritin from 359 to 175 ng/mL, and CRP from 3.04 to 1.43 mg/dL. At the end of treatment, the patient felt a marked improvement in breathing. The case presented by the authors motivates the use of PBMT as an adjuvant method in the conventional treatment of patients with severe COVID-19 and morbid obesity [34].

Reproducing the case reports mentioned above, but on a larger scale, Vetrici et al. evaluated the supporting role of PBMT for COVID-19, investigating clinical outcome and pulmonary severity indices in a small-scale study with 10 patients randomized to standard care, or the same therapy plus adjuvant PBMT, i.e., two groups that were not statistically different in terms of demographic characteristics at the beginning of the trial. The laser lot received PBMT using a near-infrared Multiwave Locked System (MLS) scanner-equipped laser (approved by the US Food and Drug Administration as a nonsignificant risk device) as daily sessions for four consecutive days to target pulmonary tissue. The laser system included two different laser arrays: (1) three GaAlAs laser diodes (808 nm), 1 W (peak power) and 500 mW (average power) for each diode, 75 mW/cm^2 power density, 330 µs each pulse; and (2) three superpulsed GaAs laser diodes (905 nm), 75 W (peak power) and 203 mW (average power) for each diode, 31 mW/cm^2 power density, 100 ns pulse duration; both arrays with the same frequency of 1500 Hz (train pulses 90 kHz modulated at 1 Hz ÷ 2 kHz), the same spot size of 19.6 cm^2 and a total energy delivered of 3590 J per session. The mobile laser scanner was 20 cm above each subject, who was lying in a prone position. The patient's clinical condition was investigated using blood tests, chest X-rays, pulse oximetry, and other standard instruments prescribed for evaluating pneumonia. Patients with PBMT were considered for ICU and intubation, but all recovered without mechanical ventilation, and all manifested a rise in oxygenation just 10 min from the onset of PBMT during each session. Three control patients had fulminant results and were intubated until day 2 due to the very fast decrease in oxygen saturation, and two of them died. At a 5-month follow-up, two of the three live control patients (one recovered spontaneously, and the other was placed on mechanical ventilation) still had severe lung-related signs. All patients with PBMT recovered without side effects or mechanical ventilation and were discharged within one week of enrollment in the study, all of whom were asymptomatic at 5 months of follow-up. Adjuvant PBMT led to an important amelioration in all investigated pulmonary indices, proving a rapid recovery, lack of hospitalization in ICU, no need for mechanical ventilation, and no long-term sequelae after 5 months after initiation of the therapy. Due to the fact that 60% of the control group were transferred to the ICU for mechanical ventilation and had an overall mortality of 40%, and another 40% suffered long-term sequelae at 5-month follow-up, compared to the good results in the PBMT group, the authors concluded that PBMT is a reliable, effective, and feasible therapy for lung inflammation in COVID-19, favorably modulating the clinical condition, avoiding the necessity for mechanical ventilation, long-term sequelae, or mortality of patients with COVID-19. The authors acknowledged that the small number of patients in the study is an important limitation for this research, and that future academic and university clinical trials with larger groups are needed to substantiate the effect of PBMT in COVID-19 [35].

Pelletier-Aouizerate et al. used red light photobiomodulation therapy (RL-PBMT) in two severe cases of COVID-19 concurrently with conventional drugs. The patients benefited from RL-PBMT through an LED device that simultaneously emitted wavelengths of 630 nm and 660 nm, respectively, applied transcutaneously, 3 sessions of 15 min each per week, at a power density of 55 mW/cm^2 with a fluence of 50 J/cm^2, on the presternal region 7 cm above the skin. Patients continued RL-PBMT for an additional 9 months post-illness to aid their recovery, particularly fatigue on exertion. RL-PBMT triggered an improvement in blood oxygenation, modulated the patients' inflammatory response, and did not induce complications during treatment. The authors recommend the use of RL-PBMT from the early stages of inflammation and respiratory pathology; this effective treatment method has a low cost and the advantage that it can be used in the clinic or at the patient's home [36].

Pereira et al. estimated the efficacy of PBMT on immunomodulatory markers and physiological parameters in COVID-19 patients at a moderate to high risk of death. 20 patients with severe COVID-19 were non-blind randomized into two groups. The laser group received six days of therapy in five areas: the lung area, face, tonsillar fossae, trachea, and bronchi. The results showed a reduction in CRP levels, a return to normal platelet counts, and a consistent improvement in partial arterial oxygen pressure (PaO_2) compared to the control group. This study proved that PBMT may be a viable option in patients diagnosed with COVID-19 who develop severe forms of the disease, including acute hypoxemic respiratory failure or ARDS, acute renal failure, and thromboembolic events, and who require hospitalization in the ICU [37].

Marashian et al. aimed to evaluate the level of pro-inflammatory cytokines to find a therapeutic strategy based on PBMT to inhibit their uncontrolled release in some patients with COVID-19, thus avoiding ICU admission or damage to vital organs. The study included 52 hospitalized patients with mild to moderate COVID-19 who were randomized into two groups (PBMT and placebo). In the group of 24 patients treated with PBMT, light was provided by 8 LEDs with wavelengths between 620–635 nm with an energy density of 45.40 J/cm^2 and a power density of 0.12 W/cm^2, twice a day, for three days, along with conventional drugs. The serum levels of the cytokines IL-6, IL-8, IL-10, and TNF-alpha were determined for both groups during the research. The results demonstrated a significant decrease in serum levels of IL-6, IL-8, and TNF-α; and the IL-6/IL-10 ratio was notably reduced in the PBMT group compared to the placebo group. In conclusion, the authors claim that the level of major cytokines (IL-6, IL-8, and TNF-α) in COVID-19 patients undergoing PBMT significantly decreased, thus paving the way for managing the cytokine storm within days [38].

Williams et al. published a non-randomized study on 50 positive COVID-19 patients using transdermal dynamic photobiomodulation of deep tissues throughout the body.

PBMT was applied by algorithmically alternating red (650 nm) and near-infrared (NIR; 850 nm) LEDs with an average power density of 11 mW/cm^2, dynamically sequenced at multiple pulse frequencies, each session of 84 min, with 20 kJ for the sinuses and 15 kJ for each lung at skin temperatures below 42 °C. The results show a significant reduction in the duration and severity of disease symptoms (fever, pain, respiratory distress with paroxysmal cough; pulmonary congestion, dyspnea, hypoxia, sinus congestion, acute ocular inflammation, and extreme malaise), which disappeared in 41/50 patients within 4 days of starting treatment, and then in 50/50 patients in the following 3 weeks, without the need for additional oxygen. SpO_2 concentrations improved by up to 9 points in all patients [39].

2.2. PBMT in Combination with Static Magnetic Field in COVID-19

PBMT as a single method or in combination with a static magnetic field (PBMT-sMF) has been confirmed in terms of beneficial effects in tissue regeneration, modulation of inflammatory processes, and improvement of pulmonary functional capacity. However, the PBMT-sMF combination as a therapeutic modality has been applied less to the respiratory tract in patients with COVID-19. Tomazoni et al. used PBMT-sMF in a case of low peripheral oxygen saturation with massive lung injury and fibrosis after COVID-19. PBMT-sMF was administered once daily for 45 days by irradiating six sites of the lower thorax and upper abdominal cavity, and two sites in the neck area. Each area was treated for 60 s, a total of 480 s per sMF session. For PBMT, 4 lasers were used that emitted at a wavelength of 905 nm, at a frequency of 250 Hz, with an output power of 50 W, and power density of 3.91 mW/cm^2—each, a dose of 0.075 J each; and 8 red LEDs (633 nm), at a frequency of 2 Hz, with a dose of 1.50 J each; as well as 8 other LEDs (850 nm), frequency of 250 Hz and output power of 40 mW. After the first 10 days of PBMT, the patient's SpO_2 increased from/to 89% to 2 L/min oxygen, and at 45 days, the patient was off supplemental oxygen, and pulmonary and radiological severity scores improved. Finally, after 4 months, the patient reached 98% SpO_2, with normal parameters of respiratory mechanics and a complete recovery [40].

De Marchi et al. conducted a prospective triple-blind randomized placebo-controlled trial in a group of 30 patients admitted to an ICU with COVID-19, who required invasive treatment, including mechanical ventilation. Patients were randomly assigned equally to two groups to receive either PBMT-sMF or a daily placebo throughout their ICU stay. PBMT was delivered via a 20-diode cluster probe that included 4 infrared diodes (905 nm, peak power: 50 W, average optical output: 1.25 mW, power density: 3.91 mW/cm^2, spot size: 0.32 cm^2, superpulsed operation mode); 8 red diodes (633 nm, average optical output: 25 mW, power density: 29.41 mW/cm^2, spot size: 0.85 cm^2 and pulsed operation mode); and another 8 infrared diodes (850 nm, average output power: 40 mW, power density: 71.23 mW/cm^2, spot size: 0.56 cm^2 and pulsed operation mode). PBMT-sMF was applied in six sites (33 cm^2 each site) in the lower thoracic/upper abdominal region, and two sites (33 cm^2 each site) in the neck area (the sternocleidomastoid muscle). The exposure time was 60 s on site, with a total treatment time of 480 s (8 min). The energy delivered to the site was 31.50 J, resulting in a total energy input of 189 J and 63 J to the lower chest and neck regions, respectively. The total irradiated surface was 264 cm^2, with a dose of 0.95 J/cm^2. The effects of PBMT-sMF in preserving respiratory muscles and modulating inflammatory processes were quantified during ICU stay, survival rate, diaphragm muscle function, ventilatory, and blood parameters, including arterial blood gas concentration. The results confirmed that the PBMT-sMF group had a shorter ICU hospital stay, no significant decrease in diaphragm thickness, improved ventilatory parameters and lymphocyte counts, and significantly lower C-reactive protein levels than the control group. There was no significant difference in ICU length of stay between the PBMT-sMF and placebo groups for severe cases of COVID-19 requiring invasive mechanical ventilation. However, PBMT-sMF is associated with increased diaphragm thickness, PaO_2/FiO_2 ratio, and lymphocyte count and decreased FiO_2, CRP levels, and hemoglobin count [41].

A summary of the studies published and presented above regarding the use of PBMT in patients with COVID-19 is presented in Table 1.

Table 1. PBMT in COVID-19 pulmonary inflammation.

Reference	Type of Study	PBMT Protocol	Monitored Parameters	Brief Results
[33] Sigman et al., 2020	Case report	Laser scanner with 2 diodes operating synchronously and simultaneously: (1) GaAlAs diode (808 nm), peak power: 3 W, pulse duration: 333 µs, dose: 7.2 J/cm^2; (2) GaAs diode (905 nm), peak power: 75 W × 3, pulse duration: 100 ns (super-pulses), dose: 113.4 mJ/cm^2. Modulation frequency = 1500 Hz, total scanned area: 25 × 10 = 250 cm^2, total energy delivered = 3600 J per session in 28 min.	Blood tests, RALE, CXR, SpO_2 and a set of questions for the patient.	PBM as adjunctive therapy in a severe case of COVID-19 pneumonia associated with ARDS, modulated the immune system, reduced inflammation and edema of lungs, and stimulated healing processes.
[34] Sigman et al., 2020	Case report	Four consecutive sessions of once-daily PBMT, dual-wavelength pulsed 808 nm laser scanner (diode GaAlAs, 3 W, frequency 1500 Hz, 330 microseconds pulse duration) and 905 nm (GaAs diode, 75 W × 3, 1500 Hz, super-pulsed 100 ns pulse duration), respectively, administered over the posterior thorax for 28 min, total delivered energy = 3600 J.	SpO_2, pulse oximetry. RALE score, Brescia-COVID indices, and SMART-COP. Levels of IL-6, serum ferritin, and CRP.	Decrease in the RALE score from 8 to 3, the Brescia-COVID indices decreased from 4 to 0, and the SMART-COP from 5 to 0. IL-6 decreased from 45.89 to 11.7 pg/mL; ferritin from 359 to 175 ng/mL, CRP from 3.04 to 1.43 mg/dL.
[35] Vetrici et al., 2021	10 patients random-ized	Two different laser arrays: (1) three GaAlAs laser diodes (808 nm), 1 W (peak power) and 500 mW (average power) for each diode, 75 mW/cm^2 power density, 330 µs each pulse; and (2) three superpulsed GaAs laser diodes (905 nm), 75 W (peak power) and 203 mW (average power) for each diode, 31 mW/cm^2 power density, 100 ns pulse duration; both arrays with the same frequency 1500 Hz (train pulses 90 kHz modulated at 1 Hz ÷ 2 kHz), the same spot size of 19.6 cm^2 and total energy 3590 J per session.	The SMART-COP score, Brescia-COVID respiratory severity scale (BCRSS), Community-Acquired Pneumonia (CAP), CXR, RALE.	Adjuvant PBMT led to an important amelioration in all investigated pulmonary indices, proving a rapid recovery, lack of hospitalization in ICU, no need for mechanical ventilation and no long-term sequelae after 5 months from initiation of the therapy.
[36] Pelletier-Aouizerate and Zivic, 2021	Two case reports	RL-PBMT through LED device that simultaneously emitted the wavelengths of 630 nm and 660 nm, applied transcutaneously, 3 sessions of 15 min each per week, power density 55 mW/cm^2 with a fluence of 50 J/cm^2, presternal region 7 cm above the skin. Patients continued RL-PBMT for an additional 9 months post-illness, particularly fatigue on exertion.	Neutrophils, ESR, serum ferritin, CRP, and CXR. Pulse oximetry.	RL-PBMT triggered an improvement in blood oxygenation, modulated the patients' inflammatory response, and did not induce complications during treatment.

Table 1. *Cont.*

Reference	Type of Study	PBMT Protocol	Monitored Parameters	Brief Results
[37] Pereira et al., 2021	20 patients with severe COVID-19, non-blind randomized into two groups (10 + 10 patients)	HILT device for PBMT—10 W. Each lung was irradiated 6 min, energy density of 8 J/cm^2, continuous mode (c.w.) on an area of 900 cm^2 and energy of 7200 J. The paranasal sinuses and nasal cavity were irradiated for 32 s, energy density of 8 J/cm^2 in c.w., hand applicator, totaling 40 cm^2 and 320 J. Trachea and bronchi regions were irradiated for two minutes, energy density 8 J/cm^2 in c.w. mode, manual applicator, totaling 150 cm^2 and 1200 J. Total treatment time 15:04 min, total area 1130 cm^2 and total energy 9040 J.	Blood values: albumin, direct bilirubin, serum bicarbonate, total bilirubin, creatinine, D- dimer, fibrinogen, hematocrit, and hemoglobin. Lactate, LDH, leukocytes, magnesium, pH, platelets, K, partial pressure of carbon dioxide, PO2, CRP, transferrin saturation, Na, prothrombin time, troponin, and urea.	Decrease of CRP level, a return to normal platelet count and a consistent improvement in PaO_2, compared to the control group.
[38] Marashian et al., 2022	Randomized, Double-Blind, Placebo Controlled study (RCT) 52 patients with mild to moderate COVID-19	PBMT was provided by 8 LEDs with wavelengths between 620–635 nm, energy density 45.40 J/cm^2, power density 0.12 W/cm^2, twice a day, for three days, along with conventional drugs.	Serum cytokines: IL-6, IL-8, IL-10 and TNF-α; and IL-6/IL-10 ratio.	At the end of the study significant decrease in the serum levels IL-6, IL-8 and TNF-α; IL-6/IL-10 ratio was significantly reduced in the PBMT group compared to the placebo group.
[39] Williams et al., 2022	Non-randomized study on 50 positive COVID-19 patients	PBMT was applied by algorithmically alternating 650 nm and 850 nm LEDs, average power density 11 mW/cm^2, dynamically sequenced at multiple pulse frequencies, each session 84 min, 20 kJ for the sinuses and 15 kJ for each lung, skin temperatures below 42 °C.	Statistical analysis of the symptoms for COVID-19: malaise, dyspnea, cough, taste and smell loss, sinus inflammation, headaches and body aches, abdominal discomfort or cramping, fever and depressed SpO_2 levels.	Duration and severity of clinical symptoms resolved in 41/50 patients within 4 days of starting treatment, and then in 50/50 patients within 3 weeks, without the need for supplemental oxygen. SpO_2 concentrations improved by up to 9 points in all patients.
[40] Tomazoni et al., 2021	Case report with low peripheral oxygen saturation, massive lung injury and fibrosis after COVID-19.	PBMT-sMF: 4 lasers: 905 nm, frequency 250 Hz, output power 50W, power density 3.91 mW/cm^2—each, dose of 0.075 J each; 8 red LEDs (633 nm), frequency 2 Hz, dose 1.50J each; 8 other LEDs (850 nm), frequency 250 Hz, output power of 40 mW. Six sites were irradiated: lower chest and upper abdominal cavity and two sites in the neck area for 60 s, totaling 480 s per session.	SpO_2; RALE score; Radiological findings at baseline, 10 days after intervention and 4 months follow-up.	After 4 months the patient reached 98% SpO_2, with normal parameters of respiratory mechanics and a complete recovery.

Table 1. *Cont.*

Reference	Type of Study	PBMT Protocol	Monitored Parameters	Brief Results
[41] De Marchi et al., 2021	Triple-blind randomized placebo-controlled trial 30 patients admitted to an ICU with COVID-19	20-diode cluster probe that included 4 IR diodes (905 nm, peak power: 50 W, average optical output: 1.25 mW, power density: 3.91 mW/cm^2, spot size: 0.32 cm^2, superpulsed operation mode); 8 red diodes (633 nm, average optical output: 25 mW, power density: 29.41mW/cm^2, spot size: 0.85 cm^2 and pulsed operation mode); and 8 IR diodes (850 nm, average output power: 40 mW, power density: 71.23 mW/cm^2, spot size: 0.56 cm^2, pulsed operation mode). PBMT-sMF was applied in six sites in the lower thoracic/upper abdominal region, two sites in the neck area. Total surface 264 cm^2, dose 0.95 J/cm^2. Energy delivered 31.50 J.	Length of ICU stay by the number of days of ICU admission from randomization to discharge or death from any cause; survival rate; diaphragm thickness; blood parameters. Mechanical ventilation parameters: PEEP (positive end-expiratory pressure), FiO_2 (fraction of inspired oxygen). Arterial blood gases: PaO_2; PaO_2/FiO_2 ratio	There was no significant difference in ICU length of stay between the PBMT-sMF and placebo groups for severe cases of COVID-19 requiring invasive mechanical ventilation. PBMT-sMF is associated with increased diaphragm thickness, PaO_2/FiO_2 ratio, and lymphocyte count and decreased FiO_2, CRP levels, and hemoglobin count.

2.3. PBMT Applied in Olfactory and Taste Dysfunctions Caused by COVID-19

Intranasal irradiation could provide neuroprotection through anti-inflammatory and antioxidant pathways due to abundant blood capillaries but with relatively slow blood flow; other possible mechanisms of action include activation of neural stem cells in the olfactory nerve, bulb, and endothelium, as well as the autonomic nervous and lymphatic systems, as Salehpour et al., argues [42].

Persistent olfactory dysfunction is often observed in many viral infections that initially affect the lining of the respiratory tract, and in SARS-CoV-2 infection, this impairment has been very common, but the pathophysiological mechanisms are not yet fully understood.

Soares et al. treated 14 cases of COVID-19 who lost their smell. PBMT was applied topically intranasally for 3 min with a laser device (660 nm, output power 100 mW, energy 18 J). The patients were divided into three groups, as follows: group 1 (5 patients received 10 laser sessions, twice a week, with a break of 48 h); group 2 (6 patients, 5 laser sessions, twice a week, with a break of 48 h); group 3 (3 patients were given 10 PBMT daily), 3 min of irradiation per nostril for each group. Finally, there was an improvement in olfactory function in all patients, regardless of PBMT protocol, but with different degrees. However, the number of cases was very small and without a control group, so the authors postulated that PBMT would be beneficial for smell recovery by modulating local inflammatory processes and improving tissue vascularity [43].

Brandão et al. presented and analyzed a series of eight cases of SARS-CoV-2 infection with necrotic mouth ulcers and aphthous-like ulcers with a loss of taste and smell. The most severe and widespread oral lesions were in the elderly, with severe forms of COVID-19. The authors hypothesize a novel etiopathogenic process between ACE-2 receptors (very present on the epithelial cells of the tongue and salivary glands) and SARS-CoV-2 in the oral cavity but admit the demand for additional studies to confirm their hypothesis and elucidate exactly the etiopathogenesis, which is still unknown. The authors applied the PBMT protocol used for patients with OM associated with cancer therapy. PBMT device (660 nm, 40 mW output power, 0.04 cm^2 beam area, 1 W/cm^2 irradiance, 0.4 J energy, and 10 J/cm^2 fluence) was positioned perpendicular to the surface of each lesion, for 10 s per site, daily for 10 consecutive days. Patients reported relief of symptoms after 2–4 days and fully recovered after all PBMT sessions. The authors acknowledge the necessity for future scientific investigations to elucidate whether SARS-CoV-2 directly infects and replicates in oral keratinocytes and fibroblasts, and generates painful oral ulcers, or whether these lesions are developing along with COVID-19. The authors also concluded that dysgeusia and early anosmia should be considered potential markers of SARS-CoV-2 infection, especially by dental staff who are highly exposed to the infection, in which case patients with such symptoms should be scheduled for consultations by telemedicine, be guided for further investigations, be immediately isolated, and have adequate medical management [44].

One of the most common symptoms reported in patients with COVID-19 was, in addition to impaired smell, the loss of taste. The pathophysiology by which viral infection disrupts tongue epithelial cells and taste receptors is not yet known. As good results have been obtained in the pathology of orofacial lesions and smell disorders, PBMT has been proposed as an easy means of restoring taste in patients with COVID-19. Campos et al. treated 10 patients with impaired taste (partial or complete) after SARS-CoV-2 infection using PBMT with a laser device emitting at 660 nm, with an output power of 100 mW and 2 J per point; a total of 7 points on the dorsal face and 3 points on each lateral edge of the tongue were treated. The results showed improvements in taste recovery for all patients [45].

Inflammation produced by SARS-CoV-2 infection is the main cause of smell and taste dysfunction in many patients. Knowing the anti-inflammatory and antioxidant effects of PBMT, de Souza et al. applied 10 sessions in the case of anosmia and ageusia related to COVID-19. The patient was treated for anosmia in the intranasal cavity with a laser device for 5 min (808 nm, output power 100 mW, beam area 3.0 mm^2, fluence 1000 J/cm^2, power density 3.33 W/cm^2 and the total energy delivered in each nostril 30 J). For the pathological loss of the sense of taste, the patient was treated with a vacuum laser without the use of the suction cup, with 6 laser beams (3 red with a wavelength of 680 nm, and 3 IR with a wavelength of 808 nm). The laser protocol parameters were as follows: power of each beam 100 mW, beam area 1.76 mm^2 (each), fluence equal to 682 J/cm^2, irradiance equal to 5.6 W/cm^2, application time 2 min on the back of the tongue and the sides of the tongue, and the inner mucosa of the cheeks, with total energy delivered to each area of 72 J, with a break of at least 48 h between sessions, over 25 days. In conclusion, the authors showed that the patient regained his olfactory and gustatory functions and considered PBMT a promising therapeutic modality, especially for sequelae related to COVID-19 [46].

Some studies presented above on the effects of PBMT in the loss of smell and taste related to COVID-19 are presented in Table 2.

Table 2. PBMT in olfactory and gustatory dysfunctions related to COVID-19.

Reference	Type of Study	PBMT Protocol	Monitored Parameters	Brief Results
[43] Soares et al., 2021	14 cases of COVID-19 who lost their smell	660 nm, output power 100 mW, 18 J energy on nasal mucosa. Group 1 (5 patients received 10 laser sessions, twice a week, with a break of 48 h); group 2 (6 patients, 5 laser sessions, twice a week, with a break of 48 h); group 3 (3 patients were given 10 PBMT, daily), 3 min of irradiation per nostril for each group.	Olfactory function on visual analog scale (VAS: 0–10).	Olfactory function was improved in all patients regardless of the PBMT protocol, but with different degrees.
[44] Brandão et al., 2021	8 cases of SARS-CoV-2 infection with necrotic mouth ulcers and aphthous-like ulcers with loss of taste and smell	PBMT (660 nm, 40 mW output power, 0.04 cm^2 beam area, 1W/cm^2 irradiance, 0.4 J energy, and fluence equal to 10 J/cm^2), applied perpendicular to the surface of each lesion, 10 s per site, daily for 10 consecutive days.	Diameter of the ulcers; local pain; anosmia; dysgeusia/ageusia	Patients reported relief of symptoms after 2–4 days and full recovery after all PBMT sessions.

Table 2. *Cont.*

Reference	Type of Study	PBMT Protocol	Monitored Parameters	Brief Results
[45] Campos et al., 2022	Case series 10 patients with impaired taste (partial or complete) after SARS-CoV-2 infection, divided in 3 groups.	660 nm; 100 mW and 2 J per point; a total of 7 points on the dorsal face and 3 points on each lateral edge of the tongue were treated. Group 1: 10 laser sessions, with a 24-h break. Group 2: 10 laser sessions, twice a week, with a 48-h break. Group 3: 5 laser sessions, twice a week, 48-h interval.	Clinical symptoms for taste perception were assessed using VAS ranging from 0 (normal taste) to 10 (complete absence of taste), before and after PBMT.	Improvements in taste recovery for all treated patients.
[46] de Souza et al., 2022	Case report The olfactory and taste dysfunction COVID-19-related (Anosmia and ageusia)	Intranasal cavity irradiated with laser for 5 min (808 nm; 100 mW, beam area 3.0 mm^2, fluence 1000 J/cm^2, power density 3.33 W/cm^2, total energy in each nostril 30 J). For ageusia Vacumlaser without the use of the suction cup: 6 laser beams [3 with red (680 nm), 3 with IR (808 nm]. Laser beam area 1.76 mm^2 (each one), power 100 mW for each laser beam, applied to the patient for 2 min on the back of the tongue and the skin surface of the cheeks, with the mouth slightly open. Total energy per area corresponds to 72 J. The fluence was 682 J/cm^2 and irradiance was 5.6 W/cm^2.	Olfactory dysfunctions (ranging to anosmia to hyposmia) and gustatory dysfunctions were measured on VAS.	The olfactory and gustatory functions were reestablished after 10 PBMT sessions.

2.4. Experimental Models Give Insight into Future Applications of PBMT

Even before the COVID-19 pandemic, numerous experimental studies supported the beneficial role of PBMT in reducing pulmonary inflammatory phenomena. Da Cunha Moraes et al. applied PBMT (diode laser, 660 nm, 30 mW, and 3 J/cm^2) for 15 days to an experimental model of chronic obstructive pulmonary disease (COPD) in C57BL/6 mice. At the end of the experiment, lung morphopathological examination showed a significant decrease in collagen deposition, P2X7 purinergic receptor expression, and the number of inflammatory cells and proinflammatory cytokines IL-1β, IL-6 and TNF-α in bronchoalveolar lavage fluid (BALF). At the same time, an increase in IL-10 was observed [47].

De Brito et al. administered PBMT (780 nm, 30 mW) to C57Bl/6 mice with experimentally induced idiopathic pulmonary fibrosis (IPF). Bleomycin-activated fibroblasts and type II pneumocytes were laser irradiated in vitro. The results showed that PBMT decreased the migration of inflammatory cells into BALF and the deposition of collagen fibers in the lungs. At the same time, PBMT decreased the total level of lung transforming growth factor beta (TGF-β) and proinflammatory cytokines and increased the secretion of IL-10 by fibroblasts and pneumocytes. PBMT reduced the number of inflammatory cells in the blood. The authors conclude that PBMT effectively reduces lung inflammation, and airway remodeling in IPF is achieved by restoring the balance between pro- and anti-inflammatory cytokines and inhibiting the secretion of pro-fibrotic cytokines by fibroblasts [48].

Zupin et al. published an article on an in vitro SARS-CoV-2 infection model in which PBM was experimentally applied with blue light-emitting diodes (450, 454, and 470 nm LEDs) with an output power of 40 mW/cm^2, continuous wave, trying the following protocol: they first irradiated the virus, then transferred the SARS-CoV-2 into the cells; second, the cells were irradiated immediately after they had already been infected; and in the third case, the cells received PBMT before infection. The results showed that for all three blue wavelengths applied, there was a decrease in the viral load, particularly when previously infected cells were irradiated, but the effects were mostly prominent at 48 h post-infection, suggesting that blue light could interfere with the intracellular viral replication. The authors claimed that this experiment could be the kick-off for the translational use of PBMT in the fight against SARS-CoV-2 infection [49].

Wajih et al. performed an experimental study on human blood using nitrites and a light source through an "intense red" LED device at a wavelength of 660 nm. In all samples, the combination of far-red light and nitrite treatment reduced platelet adhesion and coagulation compared to samples in which only monotherapy (nitrite or light) was used. The authors stated that combined far-red light and nitrite treatment can prevent thrombosis when extracorporeal devices are used, for example, in COVID-19, and would be advantageous in suppressing thrombosis in patients infected with SARS-CoV-2 [50].

In an experimental study on the culture of human embryonic kidney HEK293 cells exposed to LED light sources with a wavelength between 720 and 750 nm for 10 min, twice a day, Aguida et al. attempted to demonstrate the effect of reducing the toll-like receptor 4 (TLR-4)-dependent inflammatory response, which is involved in triggering a cytokine storm in patients with COVID-19. In this study, the authors illustrated by experiment that exposure to infrared light can decrease inflammation in response to TLR-4, dependent on innate immunity, in a human cell culture model. Only 48 h after infrared light treatment, a significant decrease in the activity of nuclear factor-κB (NF-κB) and activator protein 1 (AP-1) was observed, decreased expression of inflammatory marker genes IL-6, IL-8, TNF-α, IFN-α and IFN-β and an 80% drop in the production of IL-6, as measured by ELISA in cultured human cells. The authors hypothesized that these phenomena could be explained by modulating ROS by downward regulation of the host's immune response after exposure to infrared light, which leads to decreased inflammation.

The authors "further discussed technical considerations involving light sources and exposure conditions to put their observations into potential clinical use to treat COVID-19" [51].

Pooam et al. hypothesized that excessive inflammation and overproduction of cytokines in the lungs lead to a "cytokine storm" and acute respiratory failure during SARS-CoV-2 infection, which would have a fundamental mechanism controlled by the TLR4 signaling pathway and ROS. In an experimental study on human embryonic kidney HEK293 cell cultures, the authors investigated the inflammatory response through the up-mentioned signaling pathways by exposing the cells to PBMT and pulsed electromagnetic fields. PBMT was initiated by exposing the cell cultures to infrared (IR) light (720 nm) with an array containing 7 LEDs with an output power of 780 mW for 10 min at an interval of 12 h for a total time of 48 h. At the same time, two types of electromagnetic fields were used: low-level static magnetic field (LLF) and pulsed electromagnetic field (PEMF). LLF with an intensity of 2 microtesla (μT) was administered either for 10 min every 12 h over a period of 48 h, or continuously for 48 h. PEMF was applied at a frequency of 10 Hz with a peak magnetic intensity of 1.7 millitesla (mT) (40 times the Earth's magnetic field) over a 10-min stimulation period and administered repetitively every 12 h for 48 h. The control cells were grown in an identical manner and incubated with 100 ng/mL bacterial lipopolysaccharide (LPS), but not exposed to LLF, PEMF, or IR stimulation. PBMT cells (which included both LPS-stimulated and non-LPS-stimulated cultures) were exposed to IR pulses with a power density of 6 W/m^2 for 10 min at 12-h intervals over a period of two-day growth. Effects after LPS induction in the IR-, PEMF-, or LLF-treated groups were compared to the untreated control cells that had received LPS stimulation. The results of the study showed that IR PBMT and exposure to electromagnetic fields significantly decreased inflammation in human embryonic kidney cell cultures. Finally, since PBM and electromagnetic field procedures have no known side effects yet and are already licensed for certain medical applications, the authors designed a protocol to test the hypothesis through clinical trials of acute respiratory distress in patients with COVID-19, both at home and in the hospital [52].

In a randomized experimental model on twenty-four male Wistar rats, Macedo et al. investigated the effects of PBMT (as low-infrared laser therapy) on acute lung injury (ALI) experimentally induced by SARS-CoV-2 infection. The authors used laser equipment (808 nm; 30 mW; 1.68 J), and PBMT was administered to the anterior region of the trachea and ventral regions of the thorax, bilaterally, for 1 h to 24 h after induction of ALI. Histopathological examination, assessment of lung injury score, inflammatory cell count, and interleukin 1β (IL-1β) level showed that PBMT decreased inflammatory infiltrates, reduced alveolar septal thickness, decreased lung injury score and IL-1β immunoexpression compared to the control group [53].

The experimental models presented above to provide insight into possible future applications of PBMT in COVID-19 are shown in Table 3.

Table 3. Experimental models for PBMT as future applications in COVID-19.

Reference	Type of Study	PBMT Protocol	Monitored Parameters	Brief Results
[47] da Cunha Moraes et al., 2018	Mouse model of COPD (C57BL/6 mice)	Diode laser (660 nm, 30 mW and 3 J/cm^2) for 15 days administered to three experimental groups: basal (mice exposed to ambient air), COPD (animals exposed to cigarette smoke without LLLT), and COPD + LLLT.	Levels of IL-1β, IL-6, IL-17, TNF-α, and IL-10 were assessed in BALF supernatants; peribronchial inflammation analysis; airway remodeling assessment by collagen deposition; destruction of alveolar septa.	Histopathological examination: significant decrease in collagen deposition, P2X7 purinergic receptor expression, and the number of inflammatory cells and proinflammatory cytokines IL-1β, IL-6 and TNF-α in BALF.
[48] de Brito et al., 2020	Experimental model of IPF in C57Bl/6 mice	Irradiated (780 nm and 30 mW) and euthanized fifteen days after bleomycin-induced lung fibrosis (bleomycin-activated fibroblasts and type II pneumocytes were laser irradiated in vitro).	Number of inflammatory cells in the blood and in BALF; deposition of collagen fibers in the lungs, the pro- and anti-inflammatory cytokines, such as growth factor beta (TGF-β), proinflammatory cytokines, IL-10 secretion by fibroblasts and pneumocytes	PBMT reduced lung inflammation and airway remodeling in IPF, restored the balance between pro- and anti-inflammatory cytokines, and inhibited the secretion of pro-fibrotic cytokines by fibroblasts.
[49] Zupin et al., 2021	Experimental study on the Vero E6 epithelial normal cell line derived from the kidney of Cercopithecus aethiops (ATCC CRL-1586), in vitro model of SARS-CoV-2 infection.	PBMT: 3 blue LEDs (450 nm, 12.5 J/cm^2; 454 nm, 10 J/cm^2; and 470 nm, 20 J/cm^2); 40 mW/cm^2 output power, c.w. 3 different protocols: 1. First, the virus was irradiated, and then it was transferred into the cells. 2. Second, the cells were irradiated immediately after they had already been infected. 3. Cells received PBMT before infection.	Viral load was quantified from the supernatants and reported as Log10 viral copies/mL	This experiment could be the beginning of the translational use of PBMT in the fight against SARS-CoV-2 infection.

Table 3. *Cont.*

Reference	Type of Study	PBMT Protocol	Monitored Parameters	Brief Results
[50] Wajih et al., 2021	Experimental study on human blood	Whole blood was collected by venipuncture from healthy volunteers. A "deep red" LED source at 660 nm (560 mW output power) was used to illuminate the samples.	Platelet and RBCs mixtures were incubated at 21 °C, with and without nitrite (10 μM), and with and without PBM for 5 min followed by addition of a platelet agonist to initiate activation.	While both nitrite and far-red light illumination have inhibitory effects on platelet activity and clotting, the combination of the two has the most consistent and strongest effects. Far red light and nitrite treatment may prevent thrombosis in patients with extracorporeal devices in COVID-19.
[51] Aguida et al., 2021	Experimental model on human embryonic kidney HEK293 cell cultures	Irradiation 10 min, twice a day with an interchangeably 7-LED high output LED array (720 nm); high output LED infrared floodlights or bulbs, and a 50 W incandescent bulb, placed 20 cm above the culture plate. Wavelength range of all LED light sources 720–750 nm. The control condition was performed in an identical manner (inflammation was induced with 100 ng/mL LPS), except that cells were cultured in the incubator without infrared illumination.	qPCR analysis of altered gene expression for IL-6, IL-8, TNF-α, IFN-α and IFN-β. Activity of nuclear factor-κB (NF-κB) and activator protein 1 (AP-1).	Downregulation of the host's immune response after exposure to IR light could be explained by the release of ROS at the cellular level, which leads to decreased inflammation.
[52] Pooam et al., 2021	Experimental model on human embryonic kidney HEK293 cell cultures	Array with 7 LEDs (720 nm, output power 780 mW) for 10 min at an interval of 12 h for a total time of 48 h. LLF 2 μT, administered either 10 min every 12 h over a period of 48 h, or continuously 48 h. PEMF was applied at a frequency of 10 Hz with a peak magnetic intensity of 1.7 mT over a 10 min stimulation period, every 12 h for 48 h.	The effect of IR light exposure on the HEK-TLR4 (human embryonic kidney HEK293 cell lines stably expressing human TLR4) inflammatory response.	IR PBMT and electromagnetic field exposure significantly reduced inflammation in human cell cultures related to the pathology induced by COVID-19.

Table 3. *Cont.*

Reference	Type of Study	PBMT Protocol	Monitored Parameters	Brief Results
[53] Macedo et al., 2022	Randomized experimental model on 24 male Wistar rats	PBMT (808 nm; 30 mW), 56 s irradiation time, 0.028 cm^2 spot area, 60 J/cm^2, irradiance 1.07 W/cm^2, and 1.68 J total energy per point/section. ALI experimentally induced by SARS-CoV-2 infection. PBMT administered to the anterior region of the trachea and the ventral regions of the thorax, bilaterally, for 1 h to 24 h after induction of ALI.	Histopathological examination; morphometric evaluation of inflammatory cells; immunohistochemistry analysis; lung injury score.	PBMT reduced inflammatory infiltrates, alveolar septal thickness, lung injury score, and IL-1β immune expression compared with the ALI control group.

3. PBMT and Antimicrobial Photodynamic Therapy in the COVID Era

Photodynamic therapy (PDT) is an extensively used technology nowadays incorporating the latest applications in antibacterial, antiviral, and cancer treatments. It comprises light, a chemical compound, the photosensitizer that makes cells more sensitive or reactive to light, and in the presence of tissue, molecular oxygen induces inactivation of microorganisms or cell death through generated ROS, i.e., phototoxicity [54].

Simultaneously, the avalanche of cell death mechanisms is counterbalanced by adaptive stress responses to preserve homeostasis.

Antimicrobial photodynamic therapy (aPDT) acts instantly locally throughout the illuminated cell mass and is followed by crucial systemic immune activation, making PDT a pertinent option [55].

In the current pandemic, it was assumed that aPDT could be a good choice. Its photosensitizers are already recognized as effective, safe, and inexpensive, such as methylene blue (MB).

It might be used to disinfect clinical settings (surfaces, air, wastewater) and to prevent or reduce infections. Light sources could be artificial and/or sunlight [56].

Treatment of the upper airways in COVID-19 by aPDT with MB in the early stages of infection can reduce the viral load, favoring recovery and reducing the spread of the disease. As published by Lobo et al., RNA damage of SARS-CoV-2 can be achieved in less than 5 min at low micromolar concentrations of MB and a light energy of only 25.8 J, non-toxic for human cells at such short incubation times [57].

In a communication published in 2020, Faria et al. wrote about the importance of new approaches for the treatment of oral mucositis (OM) during the COVID-19 pandemic. The authors highlighted the importance of preventing and treating OM in patients diagnosed with advanced cancer by applying extraoral PBMT, which is safe, non-invasive, and painless, and can help a lot, keeping away from possible infections due to other intraoral maneuvers that cause much harm and suffering [58].

In this scenario, the cancer care facilities had to choose between options for maintaining cancer management during the COVID-19 pandemic, as outcomes in these patients are extremely important challenges. To reduce the transmission of SARS-CoV-2 infection to both patients and healthcare workers, the authors proposed a safe and effective working protocol for the management of OM with a closed mouth extraoral PBMT technique, providing minimal discomfort to patients and less professional exposure. The PBMT protocol used an LED cluster probe with 69 red and infrared diodes and a total power of 1390 mW to be positioned in 5 treatment places: three on the face (right, center, and left) and two on the neck (right and left), 60 s per location (50 mW/cm^2 $\times$ 60 s = 3.0 J/cm^2 for each positioning). Extraoral PBMT for OM is not completely new, but many other protocols have focused on intraoral PBMT. The authors eventually mentioned that although they could not yet provide clinical data, they felt that their shared experience could motivate the application of other new treatment protocols to protect cancer patients, physicians, and other healthcare professionals in the COVID-19 pandemic [58].

The most serious complications of COVID-19 may require intensive care and mechanical ventilation, especially in patients diagnosed with cancer who have a suppressed immune system due to various prescribed anti-cancer therapies and have an increased risk of COVID-19 infection and a mortality of over 3.5 times higher in cases of contracting the infection [59–61].

A retrospective study of 472 patients with severe COVID-19 who were admitted to the ICU and intubated lying face downward for a long time to manage breathing difficulties was published by Paula Eduardo et al. The oral medicine team applied a PBM preventive protocol for traumatic oral lesions related to orotracheal intubation (OTI) for 60 patients, which proved useful and successful, accelerating the healing of the oral mucosa, and preventing progression to lip necrosis, in addition to other useful measures, such as moisturizing the lips with vitamin E cream or saline solution, and changing the position of the intubation device when necessary. The greatest number of patients with traumatic lip injuries associated with OTI were men (67%, i.e., 40 out of 60), with a mean age of 69 years and a mean intubation time of 16.5 days. Of these, 9 (15%) had hematoma and 51 (85%) had ulcers, but their evolution was not associated with lip damage or tissue loss. PBMT was applied to the earliest signs of damage to the oral mucosa or lips once a day, with a red diode laser (660 nm, 100 mW, c.w.), in contact mode, point by point, as follows: 1 J, 10 s, 11.1 J/cm^2 per point, and 0.09 cm^2 spot area. The number of points was variable to cover the entire damaged area, to manage inflammation and tissue regeneration, and to hinder necrosis. PBM management has been shown to be effective in remarkably stopping the progression of traumatic lesions to necrosis and associated tissue loss due to OTI, thus increasing the quality of life of these patients [62].

In a comment published, Kumar S. highlighted that oral manifestations are likely to take place in advance together with loss of taste and smell in some patients with SARS-CoV-2 infection and may be a valuable early indication for COVID-19, so rapid follow-up testing is recommended [63].

In a published case report, Ramires et al. emphasized the need for further studies to elucidate the prevalence and etiology of oral manifestations of SARS-CoV-2 infection, for which many articles have been published, but the issues are yet unelucidated. The clinical signs and symptoms of oral disorders in COVID-19 cases are very different and mixed, and the published therapy protocols vary widely. The authors present a protocol of PBMT and aPDT that treated with immediate positive effects a patient diagnosed with COVID-19 and extensive lip damage without systemic drug administration. The case fully healed after only two sessions of aPDT and one PBMT session, with adequate recovery of orofacial functions in just four days. The protocol for aPDT was performed for 2 days using 0.01% MB over all lesions. Laser irradiation (660 nm, 100 mW, contact mode, point by point, 32.14 J/cm^2; 9 J and 9 s per point) was applied for a total of 30 points. The next day, PBMT was performed using the same equipment but applying an energy density equal to 17.8 J/cm^2; 1 J and 10 s of irradiation per point, and the exchange of wavelengths between 660 nm and 808 nm through a program every 5 s. After 4 days from the initiation of this protocol, the patient was fully cured, without lip lesions. The authors concluded that this combined treatment of PBMT plus aPDT initiates new approaches for the treatment of lip and mouth disorders under COVID-19 but should be continued with several clinical trials to be extensively certified and widely attested, given the obvious lack of information regarding the multiple oral manifestations of SARS-CoV-2 infection [64].

Although there are a multitude of possible options for treating orofacial lesions according to medical published works, Teixeira et al. highlighted the lack of standard protocols and proven efficacy and therefore aimed to present more cases of COVID-19 treated by combined management of aPDT and PBMT. A red laser (660 nm, 100 mW) was used for a combined PBMT and aPDT protocol, 33 J/cm^2, 0.5 J, and 5 s per point, in 6-point contact, followed by aPDT with 0.01% MB above all lesions, and after 3 min with the same laser, each lesion was irradiated 40 s (4 J). A clear advance in healing took place the next day, and after 3 days, the healing was complete. The results were good in terms of tissue regeneration and pain relief, obtained quickly in just several days, with adequate recovery of affected oral and facial functions. Therefore, the authors concluded that this series of four published cases could fill the data lack of mixed management of aPDT and PBMT, proven to be synergistically beneficial for orofacial lesions in COVID-19 cases [65].

Due to the acute lack of knowledge regarding all the signs and symptoms of initial consultations, as well as the accessible treatment choices in patients infected with the SARS-CoV-2 virus, Berlingieri et al. published a case report on opportunistic infections affecting the oral cavity in COVID-19. The authors presented the case of an 88-year-old woman without comorbidities, later confirmed by RT-PCR test for SARS-CoV-2 infection, who presented with flu-like symptoms and developed two opportunistic oral infections, namely oral pseudomembranous candidiasis, and recurrent herpes. In spite of the pain when opening the mouth and the obvious change in general condition, aPDT was applied with 0.01% MB spray solution on all regions of the mouth, and after 5 min 43 points were irradiated (oral mucosa and labial ulcers), 10 s per point (1 J) with red laser (660 nm, 100 mW), protocol repeated the next day, due to the release of the pain felt by the patient. On the third day, aPDT was performed with higher energy irradiation: 5 J and 50 s per point on the oral mucosa, in combination with PBMT (660 nm, 100 mW) applied on lips with crust already, 1 J and 10 s per point. The patient no longer reported mouth pain, had only a small number of intraoral lesions, and recovered completely on the seventh day. The authors pointed out that important disparities in scientific acquaintances and understanding of all pathophysiological mechanisms of COVID-19 have advanced such combined protocols of aPDT and PBMT, which look very encouraging to manage associated COVID-19 viral and fungal opportunistic oral infections [66].

In a series of cases, Sachet et al. highlighted the clinical presentation and specificity of three cases with COVID-19 and orofacial lesions in which a combined protocol with aPDT and PBMT was applied, and good results were obtained within a few days. The authors started from the most common PBMT parameters for wound healing and analgesia (660 nm wavelength, 100 mW output power, 1 J energy, and 10 s per application point), and for aPDT: MB at 0.01% applied 3 min before irradiation, 100 mW output power, 4.5 J as radiant energy, and 40–50 s as irradiation time per point. The protocols for each case were applied differently for the nostrils, lips, and oral cavity using a low-level laser diode device (660 nm and 808 nm), output power 40 mW–100 mW, beam spot size at target 0.036–0.043 cm^2, the exposure time 10 s–120 s per point, the radiant energy between 1 J–4.8 J/per point, the radiant exposure 23.04 J/cm^2–120 J/cm^2, and the frequency of treatment sessions for aPDT was the first day in two cases, and the first and 2nd day in one case, with MB 0.005–0.01% as photosensitizer and pre-irradiation time equal to 3 min, as well as differentiated and individualized PBMT starting from day 1, 2 or 3, in a sequence adapted to each patient until day 7–12, with a variable number of points as was necessary for the management of every affected area. The authors recommended starting management with aPDT (one to two sessions) due to the viral nature of orofacial lesions in COVID-19, followed by PBMT until complete healing, and stressed the need for future randomized trials [67].

The combined applications of PBMT and aPDT discussed above for multifarious orofacial lesions in patients with COVID-19 are summarized in Table 4.

Table 4. PBMT and aPDT in extensive orofacial and lip lesions related to COVID-19.

Reference	Type of Study	PBMT/aPDT Protocol	Monitored Parameters	Brief Results
[62] de Paula Eduardo et al., 2021	Retrospective study of 472 patients with severe COVID-19, 60 patients with extensive oral lesions and traumatic lip necrosis were included	Diode laser (660 nm, 100 mW, c.w.) in contact mode, point by point, as follows: 1 J, 10 s, 11.1J/cm^2 per point, 0.09 cm^2 spot area. Number of points was variable to cover the entire damaged area.	The diameter of the ulcero-necrotic lesions; pain; conventional laboratory data.	PMBT remarkably stopped the progression of traumatic injuries to necrosis and associated tissue loss due to OTI, thereby increasing patients' quality of life.
[64] Ramires et al., 2021	Case report 50-year-old female, obesity, hypertension, type-2 diabetes mellitus, COVID-19, extensive lip lesions	aPDT applied for 2 days using 0.01% MB over all lesions. Laser (660 nm, 100 mW, 32.14 J/cm^2; 9 J and 9 s per point) at 30 points. The next day, PBMT was applied with the same equipment, but with an increased energy density of 17.8 J/cm^2; 1 J and 10 s of irradiation per point and switching wavelengths between 660 nm and 808 nm every 5 sec.	Painful extensive crusted ulcers on lips.	Combined treatment of PBMT and aPDT applied to extensive lip lesions in a patient suffering from COVID-19 completely healed in 4 days.
[65] Teixeira et al., 2021	4 clinical cases suffering from COVID-19 with orofacial lesions	Combined PBMT and aPDT protocol: red laser (660 nm, 100 mW) 33 J/cm^2, 0.5 J and 5 s per point, in 6-point contact, followed by aPDT with 0.01% MB above all lesions, and after 3 min with the same laser each lesion was irradiated 40 sec (4 J).	Diameter of orofacial lesions and pain.	aPDT and PBMT administered for orofacial lesions in patients with COVID-19, led to their recovery in just a few days.
[66] Berlingieri et al., 2022	Case report	aPDT was applied with 0.01% MB spray solution on all regions of the mouth, and after 5 min 43 points were irradiated (oral mucosa and labial ulcers), 10 s per point (1 J) with red laser (660 nm, 100 mW), protocol repeated the next day. Third day: aPDT was performed with higher energy irradiation: 5 J and 50 s per point on the oral mucosa, in combination with PBMT (660 nm, 100mW) applied on lips with crust already, 1 J and 10 s per point.	Pain in the mouth and labial region	An elementary and non-invasive modality based on aPDT and PBMT in a case with COVID-19 and opportunistic oral infections recovered completely on the seventh day.

Table 4. *Cont.*

Reference	Type of Study	PBMT/aPDT Protocol	Monitored Parameters	Brief Results
[67] Sachet et al., 2022	Three cases with COVID-19 and orofacial lesions	PBMT: diode laser (660 nm, 100 mW output power, 1 J energy and 10 s per application point). aPDT: MB at 0.01% applied 3 min before irradiation, 100 mW output power, 4.5 J as radiant energy, 40–50 s as irradiation time per point. Protocols for each case were applied differently for the nostrils, lips, and oral cavity using the laser diodes (660 nm and 808 nm), output power 40 mW-100 mW, beam spot size at target 0.036–0.043 cm^2, exposure time 10 s–120 s per point, radiant energy between 1 J–4.8 J/per point, radiant exposure 23.04 J/cm^2–120 J/cm^2.	Pain; difficulty in eating, drinking, and speaking.	aPDT and PBMT used for orofacial lesions in patients with COVID-19 improved these lesions within days.

4. Discussion

The current COVID-19 pandemic has spread to all countries of the world, and until now, all pharmacological treatments have had limited effectiveness, with sometimes very high costs and side effects. Several vaccines are available today, but the reluctance of the population to accept them, insufficient financial resources for low-income countries, false propaganda, as well as mutations of the SARS-CoV-2 virus create difficulties for the eradication of this infection. A continuing challenge for medicine today is the urgent imperative to find new treatments.

The application of the sun's rays for healing by the ancient Egyptians, Greeks, and Romans dates back thousands of years BC. Today, we have no doubt that light can influence the development and metabolic mechanisms on the evolutionary scale of life on Earth from single-celled microorganisms, plants, and even mammals, with multiple beneficial effects. At the beginning of the 20th century, the use of light for healing entered a new stage, from sunlight to the filtered administration of light of the sun, but also of specially constructed artificial light sources, such as fluorescent tubes, with carbon arcs, quartz lamps, etc., used in the therapy of skin diseases, wounds, ulcers, syphilis, lupus, pellagra, and tuberculosis. A new stage was initiated by the discovery of the LASER. NASA-funded space technology has achieved important results quickly and painlessly with LEDs applied to the prevention and healing of mouth ulcers in cancer patients secondary to radiotherapy and chemotherapy. Through the space program, NASA revived interest in light therapies, proving, for example, that cells irradiated with near-IR light emitted by LEDs grew 150–200% faster than non-illuminated cells. Studying the historical thread of light applications in medicine, it is strikingly obvious that PBM works [68]. Maybe it is true that "all life-forms respond to light" [30].

With respect to the action of sunlight, Whittemore conducted a study to attest to the correlation between latitude and mortality caused by COVID-19, starting from an already known aspect, namely that vitamin D is vital in the regulation of the immune system, and by exposure to the sun's UV rays, the skin synthesizes vitamin D, as well as the intensity of UV radiation is increasing as we approach the equator. Eighty-eight countries selected based on their likelihood of providing reliable data were included in the study. Using mortality rates/million inhabitants, for each country on the "Worldometer" website, an analysis was made on the correlation between mortality rates and the latitude of that country. The results showed a highly significant positive correlation between the lower mortality rates and the proximity of the analyzed country to the equator. Evidence is presented to suggest a direct correlation between sun exposure and reduced mortality. This study demonstrates the relationship between a country's latitude, vitamin D deficiency, and higher mortality from COVID-19. The author argues that further studies are needed to confirm the link between latitude and the percentage of deaths caused by COVID-19, as well as to assess the time of safe exposure to sunlight and/or oral vitamin D supplementation [69].

In a published article in 2020, Ratnesar-Shumate et al. contradicted known data from previous studies that postulated the idea that SARS-CoV-2 is stable on surfaces for long periods of time under indoor conditions. The authors demonstrated that simulated sunlight can rapidly inactivate SARS-CoV-2 from simulated saliva or culture media dried on stainless steel coupons. Ninety percent of SARS-CoV-2 was inactivated every 6.8 min in simulated saliva, and every 14.3 min in the culture media when exposed to simulated sunlight representative for the summer solstice (time at which the sun reaches its maximum) at 40° N latitude at sea level on a clear day. This work provides the first scientific demonstration that sunlight can quickly inactivate SARS-CoV-2 from contaminated surfaces and non-porous materials, and the durability and risk of contagion fluctuate remarkably between indoor and outdoor environments [70].

Sharun et al. analyzed the potential impact of sunlight in reducing SARS-CoV-2 transmissibility, morbidity, and mortality due to COVID-19. A direct and interesting relationship was observed between sun exposure time, latitude, and plasma level of vitamin D and the frequency of SARS-CoV-2 contamination, as well as the degree of severity of the disease, the percentage of patients recovered, and mortality. Sunlight through visible red radiation and infrared, but especially through ultraviolet (UV) C, B, and A, could inactivate the SARS-CoV-2 virus that is in the environment, in droplets after sneezing, on surfaces, and so on. Scientific studies have identified that populations near the equator with steady exposure to sunlight are less susceptible to vitamin D deficiency and thus less susceptible to infection [71].

In another study, Guasp et al. investigated whether there is a link between the occurrence of COVID-19 and demographic and climatological conditions in distinct regions of the world. It was observed that low levels of solar radiation are linked to the increased spread of COVID-19, where the population was denser and less exposed to solar radiation. The authors' conclusion was that reduced solar irradiance generated larger outbreaks of COVID-19, and they believe that further studies are needed on the potential protective effect of sunlight on the onset of COVID-19 [72].

Fernandes et al. started with an interesting hypothesis, such as that light could reduce lethality in cases of COVID-19. In most models regarding the spread and mortality due to SARS-CoV-2, environmental temperature is considered but not the important role of light. Published data on the mechanisms of the onset of COVID-19 revealed that the SARS-CoV-2 virus produces a systemic infection that strongly affects hematopoietic organs and hemostasis, which are light-dependent systems, especially in the field of visible and infrared regions of the electromagnetic spectrum. It has been observed that hemoglobin is low and protoporphyrin is increased in patients with COVID-19, triggering a very high concentration of iron ions in the blood, which generates very strong inflammatory processes in the whole body, followed by a very rapid increase in acute phase reactants (e.g., C-reactive protein and albumin). The unsaturated nature of the cyclic porphyrinic ring makes it easy to absorb and emit radiation in the visible range, a process that can be easily influenced by applying PBM in the red and near-infrared (R-NIR) range, a fact that will lead to the generation of ATP, or vitamin D in the case of exposure to ultraviolet B (UVB) radiation. ATP and vitamin D are essential factors in activating the immune system and defending against viruses. Electron excitation in photosensitive molecules, such as hemoglobin heme, will induce changes after photon absorption, fortifying the iron ionic bond, which is centered on the pyrrole ring, thus preventing the loss of heme function in terms of oxygen transport, i.e., oxyhemoglobin (HbO_2). Light absorbed by cytochrome c oxidase CCO under the influence of red and near-infrared (R-NIR) radiation will improve electron transport, regulating enzyme activity with a significant increase in oxygen consumption in tissue mitochondria, and increasing ATP production through this process. Consequently, the absorption of light in this range, i.e., by cytochrome c oxidase CCO at a wavelength of 640 nm, and porphyrin at 900 nm, could reduce the lethality produced by COVID-19 in the authors' hypothesis [73].

Nejatifard et al. reviewed the direct anti-inflammatory effect of photobiomodulation (PBM) on acute pneumonia, as the main clinical sign characterized by dyspnea in 50% of COVID-19 cases, and ARDS in about 30% of them, i.e., on lung inflammation and acute edema, neutrophil infiltration, and the massive release of pro-inflammatory cytokines as major pathological manifestations on which PBM could have a significant impact, but also its contribution to speed up tissue recovery. Among the indirect effects, the authors pointed out the control and modulation of the immune system, intensification of blood fluxes, and oxygen in other tissues under the action of PBM. The authors included only studies relevant to the inflammatory processes of the lungs and the symptoms and characteristics related to COVID-19, classified according to the PBM parameters applied to the selected tissues and their impact on animal models. PBM was applied using red diode lasers (650 and 660 nm) with an energy density in the range of 1–12.86 J/cm^2 and a power density in the range of 12.5–210 mW/cm^2, as well as infrared lasers (808 and 830 nm), with an energy density in the range of 3–20 J/cm^2 and only one specified power density of 3.571 mW/cm^2. The full conclusive picture of the action of PBM in lung viral infections described by the authors is as follows: alveolar epithelial cells infected with SARS-CoV-2 virus transmit inflammatory signals and mainly activate macrophages and neutrophils, among others, which will generate multiple pro-inflammatory cytokines and chemokines (TNF-α, IL-1β, IL-6, ICAM -1, MIP-2, iNOS, ROS, etc.), as well as anti-inflammatory cytokines (IL-10), which can lead to cytokine storm, respiratory failure, shock, or multiorgan dysfunction. By acting with PBM in the range of 650–830 nm on alveolar epithelial cells, there is a decrease in the above-mentioned proinflammatory cytokines and chemokines, and an increase in anti-inflammatory IL-10, which will stop the possible cytokine storm, decrease the inflammatory processes, facilitate a higher oxygenation, and tissue regeneration. The authors justify the application of transthoracic PBM by direct irradiation of the lungs through the skin of the chest or back when the patient lies in a prone position, but also irradiation of the interchondral space, arguing that it has been shown that High Intensity Laser Therapy (HILT) can be useful by penetrating deeper into the lung tissue and can non-invasively reduce inflammation without long-term toxicity, genetic mutations, or other organ damage, being useful to immunocompromised patients. The second approach is the intravenous route (performed intravenously, transmucosally, or transcutaneously on superficial arteries), which will raise the oxygen carried by erythrocytes and control the biomarkers so that secondarily it will decrease the inflammation and contribute to the rejuvenation of the affected tissues. From the studies analyzed, the authors concluded that PBM at an energy density of 6.5–7.5 J/cm^2 for red lasers and 9.5–10.5 J/cm^2 for infrared lasers could be applied to reduce inflammation in the lungs, decrease neutrophil recruiting, and modulate the balance of proinflammatory and anti-inflammatory cytokines [74].

Enwemeka et al. presented the profile of phototherapy with its huge potential to reduce the impact of coronavirus disease and evoked the ways in which modern technologies in the laser industry can be easily introduced into health to fight COVID-19 and other infections. As the authors pointed out, the diversification of light application technologies and the expansion of photobiomodulation (PBM) in multiple fields of science and medicine allowed for the advantages of using light spectra—in particular, purple/blue light, red, and near infrared light. Light emitted in the blue field (400–470 nm) through various devices has antimicrobial effects; it can also act on opportunistic agents and even viral infections, including SARS-CoV-2 [75–78].

Laboratory and clinical research have shown that red and near-infrared light (600–700 nm and 700–1000 nm) could reduce lung inflammation and fibrosis, so they have beneficial effects on ARDS, the main cause of death in the COVID-19 pandemic [48,53,79].

The ubiquity of laser emitting devices, as well as LEDs, provides light-based, easy-to-achieve, low-cost, side-effect-free systems for the treatment of various diseases, including SARS-CoV-2, the disinfection of hospital machines and equipment, treatment rooms, and the environment [80,81].

Liebert et al. propose another variant of PBM treatment on the axis of the intestinal microbiome—lung for patients with severe SARS-CoV-2 infection but also for those whose recovery is delayed or those who are left with post-infectious sequelae. This approach is supported by recent publications on the efficacy of PBMT in modulating and restoring the intestinal microbiome to normality in more vulnerable patients [82].

The interrelationship between the gut's microbiome, the brain, and Parkinson's disease (PD), as well as the type of clinical expression of SARS-CoV-2 infection on the gut-lung-brain axis, is already known. PBMT applied in animal models improved PD symptoms [83] and protected neurons from degradation when used directly on the cephalic extremity [84,85], or on other areas of the body (e.g., the abdomen). Liebert et al. aimed to evaluate whether the application of remote PBMT has an influence on the reduction of clinical manifestations of PD. The authors treated seven patients with PBMT applied to the abdomen and neck region three times per week for 12 weeks in a clinical setting. PBMT was continued for 33 weeks at home. Parameters monitored included mobility, balance, cognition, fine motor skills, and sense of smell.

Individual improvements in mobility, cognition, dynamic balance, spiral test, and sense of smell were achieved by PBMT, less so in some participants during PBMT-at-home procedures when they were stuck at home due to the COVID-19 pandemic. The administration of PBMT at a distance from the cephalic extremity has been shown to be effective for a range of clinical signs in PD, with some improved symptoms being maintained up to 45 weeks despite home isolation restrictions [86].

Amaroli et al. reviewed the interaction between light and molecules that became photoacceptors during the evolution of life, going all the way to mitochondria, which had an important impact on modeling the functions of eukaryotic cells. Therefore, visible, and near-infrared PBM could influence bacterial multiplication rate, metabolism, homeostasis, stress defense, and fundamental survival mechanisms. However, the data in the literature are not sufficient for the application of well-defined PBM protocols, but they have motivated the need for in-depth studies of the interactions between light, bacteria, and the management of oral and periodontal microbiota for the health of patients [87].

Updated knowledge of the molecular and cellular mechanisms involved in the balance between microbiota and the immune system for introspection on the gut–lung–brain axis could reveal the latest benefits and perspectives of applied photobiomics for health. There is an urgent need to seek and develop innovative PBMT to successfully interact with the microbiota and the human immune system in the coronavirus crisis [88].

PBMT was applied in human medicine in the case of various chronic and degenerative diseases, in the temporary reduction of pain, lymphedema, cellulite therapy, rejuvenation, and hair recovery. PBMT is also successfully used in veterinary medicine for multiple conditions, including lower respiratory tract disorders [89–94].

Mokmeli et al. published a paper that encourages and proposes a model for the use of PBMT (or LLLT in the old terminology) in the treatment of COVID-19. Significant anti-inflammatory effects confirmed by meta-analysis are reviewed (cellular studies and animal studies) to compare the anti-inflammatory effects of drugs with PBMT in reducing pain, tendinopathy, wound healing, etc. The reducing impact of PBMT on pulmonary inflammatory phenomena has been confirmed by numerous experimental animal studies, where the beneficial effect on the extinction of cytokine storms has been demonstrated by decreasing the concentrations of proinflammatory chemokines and interleukins, especially IL-6 and TNF-α [95].

PBMT may be effective in COVID-19 infection because if applied to the anterior and posterior thorax, the absorbed light reduces systemic inflammation and coagulation disorders from the "cytokine storm" associated with COVID-19. To date, there are sufficient experimental data to support the influence of PBMT on COVID-19, and light-based strategies should be re-proposed to combat this pandemic [26,50].

De Matos et al. conducted a systematic review of articles published between 2020 and 2021 on the effects of PBMT in patients with COVID-19. Although there were few published studies at that time, the results showed that PBMT may benefit patients with COVID-19 by modulating the immune system, reducing inflammation, and restoring health [96]. The biostimulant effect is achieved at a minimum therapeutic dose of 0.01 J/cm^2 for red and infrared laser radiation, and for the ultraviolet, blue, and green regions, a minimum dose of 0.001 J/cm^2 is beneficial. However, effective stimulation is acquired at 1 J/cm^2, and doses bigger than 10 J/cm^2 could produce inhibitory effects [97], favorable in avoiding, minimizing, or even suppressing the cytokine storm [95].

Kitchen et al. investigated data from the literature on cellular and molecular mechanisms, as well as the arguments for the use of PBMT with a special wavelength of 1068 nm as therapy for patients with COVID-19. The authors highlighted the action of PBMT with 1068 nm in the release of NO, regulation of heat shock protein 70 (Hsp70), cytoprotection, improvement of blood flow, and modulation of inflammation. NO and Hsp70 are essential molecules released by 1068 nm PBMT in preventing coronavirus replication, inducing vasodilation, increasing blood flow and ATP production, as well as triggering anti-inflammatory and antithrombotic effects. PBMT with a wavelength of 1068 nm could be applied both in the early stages (acute) or in the late stages (long COVID) of SARS-CoV-2 infection by application to the nasal mucosa, by scanning the trunk skin (lungs), or on the cephalic extremity [98].

In a recent study based on published articles on how PBMT acts on the immune system, Soheilifar et al. suggested that PBMT could be used in ARDS as an adjuvant protocol in reducing acute pulmonary inflammation because it can decrease the level of pro-inflammatory cytokines IL-1β, IL-6, IL-8, tumor necrosis factor alpha (TNF-α), and monocyte chemoattractant protein 1 (MCP1), and modulates the IL-10 balance so that the hyperimmune response and the impact of the cytokine storm are reduced. Compared to the effects of corticosteroids, PBMT does not have important side effects, does not induce a tardy response of the body to remove the virus, and does not favor subsidiary infections or a longer hospital stay [99].

Jahani Sherafat et al. reviewed publications on PBMT and its anti-inflammatory action between 2005 and 2020 to identify the effects of PBMT in patients with ARDS and to highlight its manageable role in ameliorating respiratory symptoms in severe cases of COVID-19. From a total of 818 articles, only 60 were selected, and the authors concluded that PBMT could decrease viral load and suprabacterial infections in patients with COVID-19 and control the inflammatory response, and therefore, PBMT could prevent severe or critical cases of SARS-CoV-2 infection [100].

In a recent review of the literature data, Hanna et al. mainly focused on the current molecular structure of SARS-CoV-2 and the possibilities of future therapies in patients with COVID-19. The authors drew attention to the prevention of infection by vaccination and the use of light as a current treatment procedure. Currently, there is great concern as COVID-19 continues to affect millions of people and effective antiviral drugs are lacking, so phototherapy could be considered a promising non-invasive treatment modality [101].

Chang et al. report the case of a patient with Guillain-Barré syndrome following vaccination with the Oxford-Astra-Zeneca vaccine, who was initially treated with gabapentin, prednisolone, intravenous immunoglobulins (IVIG), Xanax, and acupuncture, with no improvement in symptoms. The authors successfully modulated nociceptive signals in the peripheral nervous system by intravenous 632.8 nm intravascular laser irradiation of blood (ILIB) in 10 one-hour sessions [102].

Arnabat-Dominguez et al. analyzed the special situation of dental care clinics during this pandemic, which forced laser practitioners to deal effectively with its difficulties, in terms of dangers (high chance of becoming infected and spreading the infection), as well as the need to implement new laser treatments in safe conditions for patients, and not to close their office. All medical doctors and their collaborators had to apply measures taken worldwide, such as social distancing, fresh and efficient airing, disinfection of medical devices, instruments, and all areas and surfaces, as well as the wearing of face masks, gloves, and protective shields. The authors highlighted the appropriate preventive measures to be taken due to the distinct repercussions of the laser-tissue interaction: tissue abscission and aerosol production; caloric effects that produce vaporization and fume; increased chemical function; and the effects of PBM on cells. Proper information on all dental machine operations, the adoption of specific features and protocols to decrease aerosol and fume generation, and the utilization of high-capacity aspiration systems with very good percolation just in the vicinity of the surgical place will hinder the virus spreading during laser applications. Along with the general national medical recommendations, the authors indicated the following specific precautions regarding the use of lasers in stomatology:—lowest laser parameters, but with maximum clinical efficiency and low air flow, including correct water spraying during ablations to reduce aerosols and the dissemination of the virus;—protection of face against contamination with drops, splashes, or smoke with FFP3 masks, and of the eyes with laser goggles;—a rubber shield prevents viral contamination from the mouth and saliva;—a large-volume saliva aspiration system should be used, as close as possible to the handled area;—for smoke plums, high-volume vacuum systems must be used, as close as possible to the surgically treated area;—the treatment area should be properly ventilated and disinfected, including all dental operating areas;—all the manual parts of PBMT devices must have detachable plastic films applied to avoid any contact with the skin, mucous membranes or oral fluids;—the laser devices will be disinfected before and after use, and the handpieces and the tips will be autoclaved. Concerning PBMT's advantages and its undiscovered limitations, the authors pointed out that low-energy lasers only needed protective measures on a regular basis and could complement the usefulness of the dental procedures to highlight the critical health provocations in this pandemic [103].

Pacheco et al. critically reviewed with meta-analysis the clinical evidence on the application of PBMT and aPDT for the treatment of oral lesions in patients infected with SARS-CoV-2. After verifying an extensive literature with over 5959 titles and abstracts from the most well-known databases between December 2019 and October 2021, the authors included for analysis 5 articles with 11 published clinical cases, as satisfying their inclusion criteria ("in vivo" studies and case reports, excluding works published as letters to the editor, systematic reviews and articles not available in full), using PICO Strategy, as follows: P (Population): patients infected with SARS-CoV-2, with oral lesions treated with PBMT or aPDT; I (Intervention): patients managed with PBMT and/or aPDT; C (Comparison): likeness with patients who have not been treated with PBMT and/or aPDT; O (Outcome): monitoring for any improvement in lesions treated with PBMT and/or aPDT. The results indicated as significant the associated use of PBMT with aPDT ($p = 0.004$) and isolated only PBMT ($p = 0.005$), and a good confidence interval (7.18; 39.20) in ulcerative lesions, herpes, aphthous, erythematous, petechiae, and necrotic areas. The authors concluded that PBMT and aPDT could be effective in the treatment of oral lesions in patients infected with SARS-CoV-2 in a short period of time, but more long-term randomized clinical trials are needed to define the therapeutic strategy [104].

Weber et al. investigated whether PDT with another photosensitizer, vitamin B2 (riboflavin), and a specially designed laser/LED treatment kit could treat COVID-19 in the early stages. The study included 40 patients with COVID-19 at onset with mild symptoms (fever, dry cough, headache, heavy breathing, fatigue, etc.), randomized into two groups (20 patients each). The experimental group received PDT, and the control group only conventional therapy. PDT with riboflavin improved the clinical symptoms, reduced the viral load, and prevented hospitalization and intensive care. This method proved to be simple, efficient, low-cost, and easy to self-apply at home for mild to moderate cases [105].

Parkinson's disease, with a rising frequency of occurrence following the growth of life expectancy and potentially as a sequela of COVID-19, is a neurodegenerative pathology in continuous expansion, still without any successful treatment. Since PBMT has been applied with good results in experimental studies on animals, Liebert et al. published the results of a prospective study evaluating the efficacy of PBM in reducing clinical symptoms in PD patients in 2021. The research involved 12 participants with idiopathic PD in a randomized placebo-controlled trial (RCT) using a combination of transcranial, and remote intranasal, neck, and abdominal PBMT. Six patients were randomly assigned to a 12-week treatment period, and the remaining 6 were on the waiting list for 14 weeks to start the same protocol. In the first group, after the first 12 weeks, all participants continued home treatment with individually provided PBM treatment units. To evaluate the effectiveness, the following parameters were monitored: mobility, fine motor skills, balance, and cognition before treatment, after 4 weeks, 12 weeks, and at the end of the home protocol. After 12 weeks and up to one year after the initiation of PBMT, significant improvements in all the investigated parameters were observed without secondary, undesirable effects. PBMT used at home by the PD patient himself or by a caregiver could be a safe, effective, and low-cost therapy in the COVID era [106].

Besegato et al. analyzed from several points of view how biophotonics could help oral care clinics reduce or even eliminate the cross-transmission of SARS-CoV-2 virus in the COVID era, starting from the very definition of biophotonics as the physical science of light. This incorporates properties and transmission of photons, lasers, nano- along with biotechnologies. As a field of study for the interplay between living tissues/cells and photons, used to depict, identify, and handle biologic matter from micro- to nano-levels, it includes a multitude of operating procedures and special methods that could easier develop the successful early diagnosis of various conditions, as well as for an unprecedented novel use of theragnostics, i.e., diagnostics and therapy together, for top patient management in this pandemic. The authors highlighted that oral care staff can be found at the top of the pyramid of professional exposure risk to COVID-19 due to proximal interaction with patients and the application of aerosol-producing techniques during oral procedures. Air-suspended small particles having a size between droplets (>5 μm) and even smaller (1–5 μm) can withstand or travel in the air for hours, contaminating everything they have encountered. Therefore, face-to-face connection, droplets, and aerosols breathing in, manipulating sharp-edge tools and devices, and vulnerability to saliva and sputum, blood, and other body fluids are very high-risk factors for SARS-CoV-2 cross-infection. The authors' synthesis included various feasible biophotonics applications with their benefits and limitations, such as:—UVC light (100–260 nm) and antimicrobial blue light (405 nm) for surface and air decontamination;—PBMT (1–100 mW/cm^2) for pain relief, alleviation of oral ulcers and OM, muscle relaxation, and treatment of dentinal hypersensitivity;—high power lasers (>500 mW) for soft tissue oral surgery, caries preparation and removal; remineralization or disinfection of root canals; and aPDT for oral decontamination [107], the management of dental caries, endodontic infections, periodontal lesions, oral candidiasis, etc. Among others, regarding biosafety in dentistry in the COVID era, the most important limitations regarding PBM applications were insufficient scientific knowledge of all oral manifestations of SARS-CoV-2 infection and the lack of randomized clinical trials on safety and efficacy in patients with COVID-19, as well as the standardized protocols that are missing in the aPDT. The authors pointed out that currently available data prove that biophotonics' modus operandi could eliminate contamination of spaces, air, and tissues, decrease quantity of microbes, emission of aerosols, and the spread of the virus by non-intrusive alternative means, saving time and money. However, each situation must be particularized for those dental settings and procedures, both in terms of the usefulness and disadvantages of this new mode of action, but invariably following always inoffensive and less aerosol-producing techniques [108].

A synthesis of the main applications of light as a healing tool in COVID-19, and its benefits is depicted in Figure 1.

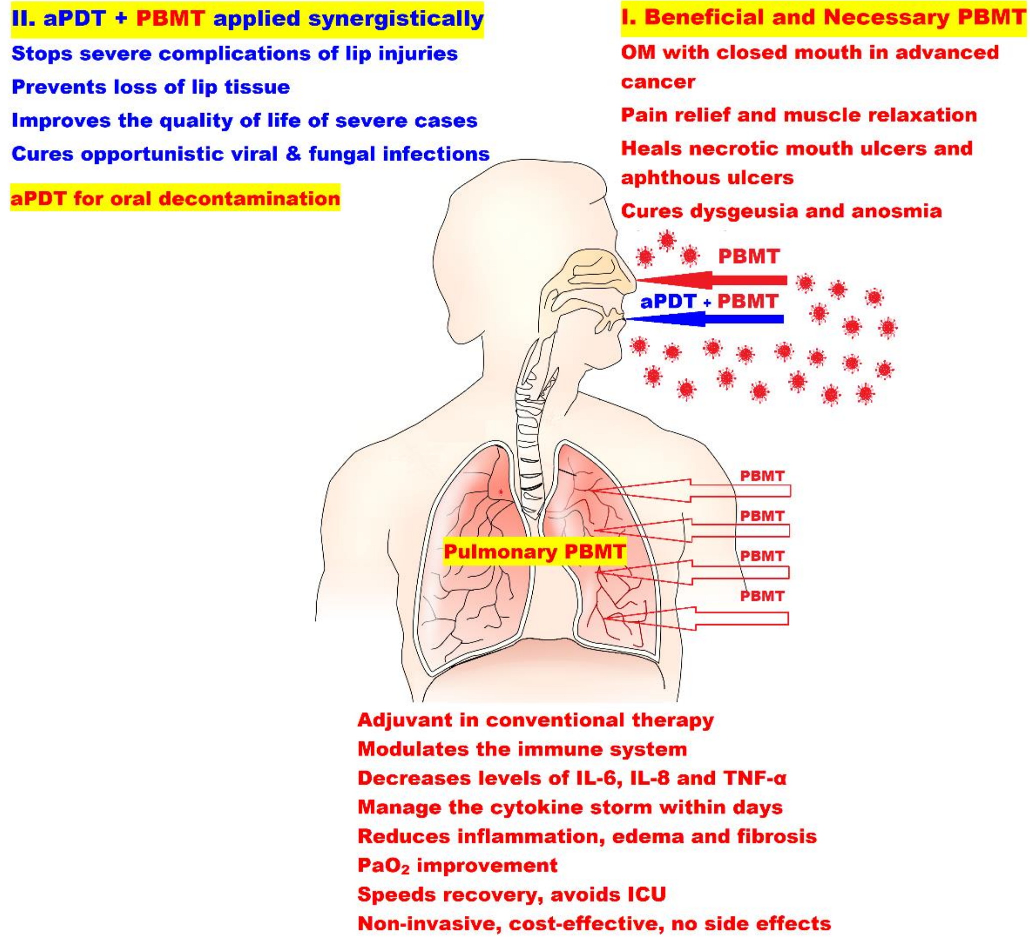

Figure 1. Management of oral, nasal, and lung conditions in COVID-19 using PBMT, or synergistically applied PBMT and aPDT. [Figure 1 was imagined and drawn by L.M.A. using Microsoft Paint 3D for Windows 10 and using completely free picture material (Open—Respiratory System Png) from SeekPNG.com (accessed on 4 June 2022), for which we are very grateful].

5. Conclusions

Complementary to allopathic treatments in COVID-19, PBMT has been successfully applied, but only in a limited number of cases, sometimes without randomization and placebo control. These PBMT studies carried out in critical pandemic conditions were a challenge for medicine and a pioneering action in SARS-CoV-2 infection and highlighted significant improvements in pulmonary inflammation and the general clinical condition of the patients, a faster recovery, avoiding hospitalization in the ICU, mechanical ventilation, mortality, and overcoming long-term sequelae.

Although PBM is a potential, safe, and efficient therapy for COVID-19, all authors recognized the important limitations of their research and the need for future randomized, placebo-controlled clinical trials with a larger number of patients to objectively determine the action and effects of the PBMT in COVID-19.

Implementation of unparallel theragnostic methods and light-based techniques for the disinfection of spaces, air, skin, mucosae, and textures to decrease the load of SARS-CoV-2 virus would save lives, time, and money for top patient management in this pandemic.

In this ongoing and challenging search for the seemingly intangible ending of this pandemic, a non-invasive, easily accessible, safe, and side-effect-free adjuvant method appears to be PBMT, alone, or in synergistic combination with aPDT, which has been proven to work in COVID-19.

Self-treatment at home with small and inexpensive low-power lasers, LEDs, or other light-based kits available for patients (preferably trained by physicians) who wish to treat their throat, mouth, and nose from the early days of infection, especially for the Omicron variant, by a non-pharmacological adjuvant method such as PBMT, would overcome unfavorable disease progression, long-term complications, saving time, money, and many lives.

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Abbreviations

Activator Protein 1	AP-1
Acute Lung Injury	ALI
Acute Respiratory Distress Syndrome	ARDS
Adenosine Triphosphate	ATP
Angiotensin-Converting Enzyme 2	ACE-2
Antimicrobial Photodynamic Therapy	aPDT
Brescia-COVID Respiratory Severity Scale	BCRSS
Bronchoalveolar Lavage Fluid	BALF
Chest X–ray	CXR
Chronic Obstructive Pulmonary Disease	COPD
Community-Acquired Pneumonia	CAP
Continuous Wave	c.w.
Coronavirus Disease 2019	COVID-19
C-Reactive Protein	CRP
Cyclic Adenosine Monophosphate	cAMP
Cytochrome C oxidase	CCO
Food and Drug Administration	FDA
Fraction of Inspired Oxygen	FiO_2
Gallium-Aluminum-Arsenide	GaAlAs
Gallium-Arsenide	GaAs
Heat Shock Protein 70	Hsp70
High Intensity Laser Therapy	HILT
Human Embryonic Kidney HEK293 Cell Lines Stably Expressing Human TLR4	HEK-TLR4
Idiopathic Pulmonary Fibrosis	IPF
Infrared	IR
Intensive Care Unit	ICU
Intercellular Adhesion Molecule-1	ICAM-1
Interferon-α, Interferon-β	IFN-α, IFN-β
Interleukin	IL-
Interleukin-1β	IL-1β
Isoforms of NO Synthase	iNOS
Intracellular Calcium Ions	Ca^{2+}
Intravascular Laser Irradiation of Blood	ILIB

Intravenous Immunoglobulins	IVIG
Joule	J
Lactate Dehydrogenase	LDH
Light Emitting Diodes	LEDs
Lipopolysaccharide	LPS
Low Level Light/Laser Therapy	LLLT
Low-Level Static Magnetic Field	LLF
Macrophage Inflammatory Protein-2	MIP-2
Methylene Blue	MB
Microtesla	μT
Middle East Respiratory Syndrome Coronavirus	MERS-CoV
Millitesla	mT
Monocyte Chemoattractant Protein 1	MCP1
Multiwave Locked System	MLS
Near-Infrared	NIR
Nitric Oxide	NO
Nuclear Factor-κB	NF-κB
Oral Mucositis	OM
Orotracheal Intubation	OTI
Oxyhemoglobin	HbO_2
Parkinson's Disease	PD
Partial Arterial Oxygen Pressure	PaO_2
Partial Pressure of Oxygen	PO_2
Peripheral Oxygen Saturation	SpO_2
Photobiomodulation	PBM
Photobiomodulation Therapy	PBMT
Photobiomodulation Therapy with Static Magnetic Field	PBMT-sMF
Photodynamic Therapy	PDT
Positive End-Expiratory Pressure	PEEP
Potassium	K
Pulsed Electromagnetic Field	PEMF
Radiographic Assessment of Lung Edema	RALE
Randomized Placebo-Controlled Trial	RCT
Reactive Oxygen Species	ROS
Red and Near-Infrared	R-NIR
Red Blood Cell	RBC
Red Light Photobiomodulation Therapy	RL-PBMT
Score for Pneumonia Severity Predicting the Need for Intensive Respiratory or Vasopressor Support (IRVS)	SMART-COP
Severe Acute Respiratory Syndrome Coronavirus	SARS-CoV
Severe Acute Respiratory Syndrome Coronavirus 2	SARS-CoV-2
Sodium	Na
Toll-Like Receptor 4	TLR4
Transforming Growth Factor Beta	TGF-β
Tumor Necrosis Factor Alpha	TNF-α
Visual Analog Scale	VAS
United Nations	UN
Ultraviolet	UV
Ultraviolet B	UVB
Ultraviolet C	UVC
World Health Organization	WHO

References

1. Andersen, K.G.; Rambaut, A.; Lipkin, W.I.; Holmes, E.C.; Garry, R.F. The proximal origin of SARS-CoV-2. *Nat. Med.* **2020**, *26*, 450–452. [CrossRef]
2. Mallah, S.I.; Ghorab, O.K.; Al-Salmi, S.; Abdellatif, O.S.; Tharmaratnam, T.; Iskandar, M.A.; Sefen, J.; Sidhu, P.; Atallah, B.; El-Lababidi, R.; et al. COVID-19: Breaking down a global health crisis. *Ann. Clin. Microbiol. Antimicrob.* **2021**, *20*, 35. [CrossRef]

3. WHO. Naming the Coronavirus Disease (COVID-19) and the Virus That Causes It. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it (accessed on 21 June 2022).
4. Siddique, F.; Abbas, R.Z.; Mansoor, M.K.; Alghamdi, E.S.; Saeed, M.; Ayaz, M.M.; Rahman, M.; Mahmood, M.S.; Iqbal, A.; Manzoor, M.; et al. An Insight Into COVID-19: A 21st Century Disaster and Its Relation to Immunocompetence and Food Antioxidants. *Front. Vet. Sci.* **2021**, *7*, 586637. [CrossRef]
5. World Development Report 2022. Finance for an Equitable Recovery. Available online: https://www.worldbank.org/en/publication/wdr2022?cid=ECR_GA_worldbank_EN_EXTP_WDR&gclid=Cj0KCQjw2MWVBhCQARIsAIjbwoPFaakDeMjr5ch6wXXFzD2JYke7F_nw-0AqQlvL374NKB1K8igyhEgaAq12EALw_wcB (accessed on 21 June 2022).
6. United Nations. COVID-19 Pandemic Stalls Global Economic Recovery: UN Report. Available online: https://news.un.org/en/story/2022/01/1109702 (accessed on 20 June 2022).
7. Statista. Number of Coronavirus (COVID-19) Cases Worldwide. Available online: https://www.statista.com/statistics/1043366/novel-coronavirus-2019ncov-cases-worldwide-by-country/ (accessed on 1 August 2022).
8. Domingo, J.L. What we know and what we need to know about the origin of SARS-CoV-2. *Environ. Res.* **2021**, *200*, 111785. [CrossRef]
9. Ailioaie, L.M.; Ailioaie, C.; Litscher, G. Implications of SARS-CoV-2 Infection in Systemic Juvenile Idiopathic Arthritis. *Int. J. Mol. Sci.* **2022**, *23*, 4268. [CrossRef]
10. Ailioaie, L.M.; Ailioaie, C.; Litscher, G.; Chiran, D.A. Celiac Disease and Targeting the Molecular Mechanisms of Autoimmunity in COVID Pandemic. *Int. J. Mol. Sci.* **2022**, *23*, 7719. [CrossRef]
11. Lazarus, J.V.; Wyka, K.; White, T.M.; Picchio, C.A.; Rabin, K.; Ratzan, S.C.; Leigh, J.P.; Hu, J.; El-Mohandes, A. Revisiting COVID-19 vaccine hesitancy around the world using data from 23 countries in 2021. *Nat. Commun.* **2022**, *13*, 3801. [CrossRef]
12. Litscher, G.; Ailioaie, L.M. Comments on New Integrative Photomedicine Equipment for Photobiomodulation and COVID-19. *Photonics* **2021**, *8*, 303. [CrossRef]
13. Finsen, N.R. *Phototherapy: (1) the Chemical Rays of Light and Small-Pox; (2) Light as a Stimulant; (3) the Treatment of Lupus Vulgaris by Concentrated Chemical Rays*; Edward, A., Ed.; Edward Arnold: London, UK, 1901; Volume 1, pp. 1–79, Internet Archive; Available online: https://archive.org/details/39002010758374.med.yale.edu (accessed on 22 July 2022).
14. Møller, K.I.; Kongshoj, B.; Philipsen, P.A.; Thomsen, V.O.; Wulf, H.C. How Finsen's light cured lupus vulgaris. *Photodermatol. Photoimmunol. Photomed.* **2005**, *21*, 118–124. [CrossRef] [PubMed]
15. Gøtzsche, P.C. Niels Finsen's treatment for lupus vulgaris. *J. R. Soc. Med.* **2011**, *104*, 41–42. [CrossRef]
16. The Nobel Prize in Physiology or Medicine 1903. NobelPrize.org. Nobel Prize Outreach AB 2022. Thu. 21 Jul 2022. Available online: https://www.nobelprize.org/prizes/medicine/1903/summary/ (accessed on 21 July 2022).
17. Mester, E.; Szende, B.; Tota, J.G. Effect of laser on hair growth of mice. *Kiserl. Orvostud.* **1967**, *19*, 628–631.
18. Mester, E.; Szende, B.; Gärtner, P. Die Wirkung der Lasstrahlen auf den Haarwuchs der Maus [The effect of laser beams on the growth of hair in mice]. *Radiobiol. Radiother.* **1968**, *9*, 621–626.
19. Anders, J.J. Photobiomodulation. American Society for Laser Medicine and Surgery (ASLMS). Available online: https://www.aslms.org/for-the-public/treatments-using-lasers-and-energy-based-devices/photobiomodulation (accessed on 26 July 2022).
20. Zein, R.; Selting, W.; Hamblin, M.R. Review of light parameters and photobiomodulation efficacy: Dive into complexity. *J. Biomed. Opt.* **2018**, *23*, 1–17. [CrossRef]
21. Anders, J.J.; Arany, P.R.; Baxter, G.D.; Lanzafame, R.J. Light-Emitting Diode Therapy and Low-Level Light Therapy Are Photobiomodulation Therapy. *Photobiomodul. Photomed. Laser Surg.* **2019**, *37*, 63–65. [CrossRef] [PubMed]
22. Moskvin, S.V. Low-Level Laser Therapy: "Western School" vs. "Eastern School". *J. Lasers Med. Sci.* **2021**, *12*, e66. [CrossRef] [PubMed]
23. Oliveira, M.C.; Greiffo, F.R., Jr.; Rigonato-Oliveira, N.C.; Custódio, R.W.; Silva, V.R.; Damaceno-Rodrigues, N.R.; Almeida, F.M.; Albertini, R.; Lopes-Martins, R.Á.; de Oliveira, L.V.; et al. Low level laser therapy reduces acute lung inflammation in a model of pulmonary and extrapulmonary LPS-induced ARDS. *J. Photochem. Photobiol. B* **2014**, *134*, 57–63. [CrossRef] [PubMed]
24. Sergio, L.; Thomé, A.; Trajano, L.; Mencalha, A.L.; da Fonseca, A.S.; de Paoli, F. Photobiomodulation prevents DNA fragmentation of alveolar epithelial cells and alters the mRNA levels of caspase 3 and Bcl-2 genes in acute lung injury. *Photochem. Photobiol. Sci.* **2018**, *17*, 975–983. [CrossRef]
25. da-Palma-Cruz, M.; da Silva, R.F.; Monteiro, D.; Rehim, H.; Grabulosa, C.C.; de Oliveira, A.; Lino-Dos-Santos-Franco, A. Photobiomodulation modulates the resolution of inflammation during acute lung injury induced by sepsis. *Lasers Med. Sci.* **2019**, *34*, 191–199. [CrossRef] [PubMed]
26. Sabino, C.P.; Ball, A.R.; Baptista, M.S.; Dai, T.; Hamblin, M.R.; Ribeiro, M.S.; Santos, A.L.; Sellera, F.P.; Tegos, G.P.; Wainwright, M. Light-based technologies for management of COVID-19 pandemic crisis. *J. Photochem. Photobiol. B* **2020**, *212*, 111999. [CrossRef] [PubMed]
27. Knowles, J.R. Enzyme-catalyzed phosphoryl transfer reactions. *Annu. Rev. Biochem.* **1980**, *49*, 877–919. [CrossRef] [PubMed]
28. Karu, T.I. Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation. *IUBMB Life* **2010**, *62*, 607–610. [CrossRef]
29. de Freitas, L.F.; Hamblin, M.R. Proposed Mechanisms of Photobiomodulation or Low-Level Light Therapy. *IEEE J. Sel. Top. Quantum. Electron.* **2016**, *22*, 7000417. [CrossRef]

30. Hamblin, M.R.; Huang, Y.Y.; Heiskanen, V. Non-mammalian Hosts and Photobiomodulation: Do All Life-forms Respond to Light? *Photochem. Photobiol.* **2019**, *95*, 126–139. [CrossRef]
31. Chung, H.; Dai, T.; Sharma, S.K.; Huang, Y.Y.; Carroll, J.D.; Hamblin, M.R. The nuts and bolts of low-level laser (light) therapy. *Ann. Biomed. Eng.* **2012**, *40*, 516–533. [CrossRef]
32. Borzabadi-Farahani, A. Effect of low-level laser irradiation on proliferation of human dental mesenchymal stem cells; a systemic review. *J. Photochem. Photobiol. B* **2016**, *162*, 577–582. [CrossRef]
33. Sigman, S.A.; Mokmeli, S.; Monici, M.; Vetrici, M.A. A 57-Year-Old African American Man with Severe COVID-19 Pneumonia Who Responded to Supportive Photobiomodulation Therapy (PBMT): First Use of PBMT in COVID-19. *Am. J. Case Rep.* **2020**, *21*, e926779. [CrossRef]
34. Sigman, S.A.; Mokmeli, S.; Vetrici, M.A. Adjunct low level laser therapy (LLLT) in a morbidly obese patient with severe COVID-19 pneumonia: A case report. *Can. J. Respir. Ther.* **2020**, *56*, 52–56. [CrossRef]
35. Vetrici, M.A.; Mokmeli, S.; Bohm, A.R.; Monici, M.; Sigman, S.A. Evaluation of Adjunctive Photobiomodulation (PBMT) for COVID-19 Pneumonia via Clinical Status and Pulmonary Severity Indices in a Preliminary Trial. *J. Inflamm. Res.* **2021**, *14*, 965–979. [CrossRef]
36. Pelletier-Aouizerate, M.; Zivic, Y. Early cases of acute infectious respiratory syndrome treated with photobiomodulation, diagnosis and intervention: Two case reports. *Clin. Case Rep.* **2021**, *9*, 2429–2437. [CrossRef]
37. Pereira, F.L.C.; Luchi, E.; Corassa, J.M.; Rossi, F.M.; da Silva Mendes, P.; de Castro Roque, E.A.; Caliari, J.S.; Pedrazas, V.S.; Pereira, V.S.; Fonseca, R.M.C.; et al. Use of photobiomodulation therapy for the evolution of immunomodulatory markers and physiological parameters in patients with Covid-19. *IJDR* **2021**, *11*, 47152–47157. [CrossRef]
38. Marashian, S.M.; Hashemian, M.; Pourabdollah, M.; Nasseri, M.; Mahmoudian, S.; Reinhart, F.; Eslaminejad, A. Photobiomodulation Improves Serum Cytokine Response in Mild to Moderate COVID-19: The First Randomized, Double-Blind, Placebo Controlled, Pilot Study. *Front. Immunol.* **2022**, *13*, 929837. [CrossRef]
39. Williams, R.K.; Raimondo, J.; Cahn, D.; Williams, A.; Schell, D. Whole-organ transdermal photobiomodulation (PBM) of COVID-19: A 50-patient case study. *J. Biophotonics* **2022**, *15*, e202100194, Erratum in *J. Biophotonics* **2022**, *15*, e202190015. [CrossRef]
40. Tomazoni, S.S.; Johnson, D.S.; Leal-Junior, E.C.P. Multi-Wavelength Photobiomodulation Therapy Combined with Static Magnetic Field on Long-Term Pulmonary Complication after COVID-19: A Case Report. *Life* **2021**, *11*, 1124. [CrossRef]
41. De Marchi, T.; Frâncio, F.; Ferlito, J.V.; Weigert, R.; de Oliveira, C.; Merlo, A.P.; Pandini, D.L.; Pasqual-Júnior, B.A.; Giovanella, D.; Tomazoni, S.S.; et al. Effects of Photobiomodulation Therapy Combined with Static Magnetic Field in Severe COVID-19 Patients Requiring Intubation: A Pragmatic Randomized Placebo-Controlled Trial. *J. Inflamm. Res.* **2021**, *14*, 3569–3585. [CrossRef] [PubMed]
42. Salehpour, F.; Gholipour-Khalili, S.; Farajdokht, F.; Kamari, F.; Walski, T.; Hamblin, M.R.; DiDuro, J.O.; Cassano, P. Therapeutic potential of intranasal photobiomodulation therapy for neurological and neuropsychiatric disorders: A narrative review. *Rev. Neurosci.* **2020**, *31*, 269–286. [CrossRef]
43. Soares, L.; Guirado, M.; Berlingieri, G.; Ramires, M.; Lyra, L.; Teixeira, I.S.; Oliveira, P.C.; Tateno, R.Y.; Palma, L.F.; Campos, L. Intranasal photobiomodulation therapy for COVID-19-related olfactory dysfunction: A Brazilian multicenter case series. *Photodiagnosis Photodyn. Ther.* **2021**, *36*, 102574. [CrossRef]
44. Brandão, T.B.; Gueiros, L.A.; Melo, T.S.; Prado-Ribeiro, A.C.; Nesrallah, A.; Prado, G.; Santos-Silva, A.R.; Migliorati, C.A. Oral lesions in patients with SARS-CoV-2 infection: Could the oral cavity be a target organ? *Oral Surg. Oral Med. Oral Pathol. Oral Radiol.* **2021**, *131*, e45–e51. [CrossRef]
45. Campos, L.; Soares, L.; Berlingieri, G.; Ramires, M.; Guirado, M.; Lyra, L.; Teixeira, I.S.; Oliveira, P.C.; Alvares, C.; Palma, L.F. A Brazilian multicenter pilot case series on the efficacy of photobiomodulation therapy for COVID-19-related taste dysfunction. *Photodiagnosis Photodyn. Ther.* **2022**, *37*, 102643. [CrossRef]
46. de Souza, V.B.; Ferreira, L.T.; Sene-Fiorese, M.; Garcia, V.; Rodrigues, T.Z.; Junior, A.E.A.; Bagnato, V.S.; Panhoca, V.H. Photobiomodulation therapy for treatment olfactory and taste dysfunction COVID-19-related: A case report. *J. Biophotonics* **2022**, *15*, e202200058. [CrossRef]
47. da Cunha Moraes, G.; Vitoretti, L.B.; de Brito, A.A.; Alves, C.E.; de Oliveira, N.; Dias, A.D.S.; Matos, Y.; Oliveira-Junior, M.C.; Oliveira, L.; da Palma, R.K.; et al. Low-Level Laser Therapy Reduces Lung Inflammation in an Experimental Model of Chronic Obstructive Pulmonary Disease Involving P2X7 Receptor. *Oxidative Med. Cell. Longev.* **2018**, *2018*, 6798238. [CrossRef]
48. de Brito, A.A.; da Silveira, E.C.; Rigonato-Oliveira, N.C.; Soares, S.S.; Brandao-Rangel, M.; Soares, C.R.; Santos, T.G.; Alves, C.E.; Herculano, K.Z.; Vieira, R.P.; et al. Low-level laser therapy attenuates lung inflammation and airway remodeling in a murine model of idiopathic pulmonary fibrosis: Relevance to cytokines secretion from lung structural cells. *J. Photochem. Photobiol. B* **2020**, *203*, 111731. [CrossRef]
49. Zupin, L.; Gratton, R.; Fontana, F.; Clemente, L.; Pascolo, L.; Ruscio, M.; Crovella, S. Blue photobiomodulation LED therapy impacts SARS-CoV-2 by limiting its replication in Vero cells. *J. Biophotonics* **2021**, *14*, e202000496. [CrossRef] [PubMed]
50. Wajih, N.; Alipour, E.; Rigal, F.; Zhu, J.; Perlegas, A.; Caudell, D.L.; Kim-Shapiro, D. Effects of nitrite and far-red light on coagulation. *Nitric Oxide* **2021**, *107*, 11–18. [CrossRef]
51. Aguida, B.; Pooam, M.; Ahmad, M.; Jourdan, N. Infrared light therapy relieves TLR-4 dependent hyper-inflammation of the type induced by COVID-19. *Commun. Integr. Biol.* **2021**, *14*, 200–211. [CrossRef] [PubMed]

52. Pooam, M.; Aguida, B.; Drahy, S.; Jourdan, N.; Ahmad, M. Therapeutic application of light and electromagnetic fields to reduce hyper-inflammation triggered by COVID-19. *Commun. Integr. Biol.* **2021**, *14*, 66–77. [CrossRef] [PubMed]
53. Macedo, D.B.; Tim, C.R.; Kido, H.W.; Macedo, J.B.; Martignago, C.; Renno, A.; Macedo, G.B.; Assis, L. Influence of photobiomodulation therapy on the treatment of pulmonary inflammatory conditions and its impact on COVID-19. *Lasers Med. Sci.* **2022**, *37*, 1921–1929. [CrossRef]
54. Ailioaie, L.M.; Ailioaie, C.; Litscher, G. Latest Innovations and Nanotechnologies with Curcumin as a Nature-Inspired Photosensitizer Applied in the Photodynamic Therapy of Cancer. *Pharmaceutics* **2021**, *13*, 1562. [CrossRef] [PubMed]
55. Donohoe, C.; Senge, M.O.; Arnaut, L.G.; Gomes-da-Silva, L.C. Cell death in photodynamic therapy: From oxidative stress to anti-tumor immunity. *Biochim. Biophys. Acta Rev. Cancer* **2019**, *1872*, 188308. [CrossRef]
56. Almeida, A.; Faustino, M.; Neves, M. Antimicrobial Photodynamic Therapy in the Control of COVID-19. *Antibiotics* **2020**, *9*, 320. [CrossRef] [PubMed]
57. Lobo, C.S.; Rodrigues-Santos, P.; Pereira, D.; Núñez, J.; Trêpa, J.; Sousa, D.L.; Lourenço, J.V.; Coelho, M.F.; de Almeida, L.P.; da Cunha, J.S.; et al. Photodynamic disinfection of SARS-CoV-2 clinical samples using a methylene blue formulation. *Photochem. Photobiol. Sci.* **2022**, *21*, 1101–1109. [CrossRef] [PubMed]
58. Faria, K.M.; Gomes-Silva, W.; Kauark-Fontes, E.; Bonfim-Alves, C.G.; Kowalski, L.P.; Prado-Ribeiro, A.C.; Vechiato-Filho, A.J.; Lopes, M.A.; Marta, G.N.; de Castro, G., Jr.; et al. Impact of pandemic COVID-19 outbreak on oral mucositis preventive and treatment protocols: New perspectives for extraoral photobiomodulation therapy. *Support Care Cancer* **2020**, *28*, 4545–4548, Erratum in *Support Care Cancer* **2021**, *29*, 4177. [CrossRef]
59. Seth, G.; Sethi, S.; Bhattarai, S.; Saini, G.; Singh, C.B.; Aneja, R. SARS-CoV-2 Infection in Cancer Patients: Effects on Disease Outcomes and Patient Prognosis. *Cancers* **2020**, *12*, 3266. [CrossRef] [PubMed]
60. Yu, J.; Ouyang, W.; Chua, M.; Xie, C. SARS-CoV-2 Transmission in Patients With Cancer at a Tertiary Care Hospital in Wuhan, China. *JAMA Oncol.* **2020**, *6*, 1108–1110. [CrossRef]
61. Liang, W.; Guan, W.; Chen, R.; Wang, W.; Li, J.; Xu, K.; Li, C.; Ai, Q.; Lu, W.; Liang, H.; et al. Cancer patients in SARS-CoV-2 infection: A nationwide analysis in China. *Lancet Oncol.* **2020**, *21*, 335–337. [CrossRef]
62. de Paula Eduardo, F.; Gobbi, M.F.; Bergamin, L.G.; Migliorati, C.A.; Bezinelli, L.M. Oral care and photobiomodulation protocol for the prevention of traumatic injuries and lip necrosis in critically ill patients with COVID-19: An observational study. *Lasers Dent. Sci.* **2021**, *5*, 239–245. [CrossRef]
63. Kumar, S. Could the oral cavity be a target organ in SARS-CoV-2 infection? *Evid. Based Dent.* **2021**, *22*, 78–79. [CrossRef]
64. Ramires, M.; Mattia, M.B.; Tateno, R.Y.; Palma, L.F.; Campos, L. A combination of phototherapy modalities for extensive lip lesions in a patient with SARS-CoV-2 infection. *Photodiagnosis Photodyn. Ther.* **2021**, *33*, 102196. [CrossRef] [PubMed]
65. Teixeira, I.S.; Leal, F.S.; Tateno, R.Y.; Palma, L.F.; Campos, L. Photobiomodulation therapy and antimicrobial photodynamic therapy for orofacial lesions in patients with COVID-19: A case series. *Photodiagnosis Photodyn. Ther.* **2021**, *34*, 102281. [CrossRef]
66. Berlingieri, G.; Alvares, C.; Serrano, R.V.; Palma, L.F.; Campos, L. Phototherapies for COVID-19-associated opportunistic oral infections. *Photodiagnosis Photodyn. Ther.* **2022**, *37*, 102678. [CrossRef] [PubMed]
67. Sachet, P.; Rocha, B.A.; Lima, F.S.; Pedrosa, M.; Guollo, A.; Filho, M.R.M.; Horta, M.; Simões, A. Management of orofacial lesions with antimicrobial photodynamic therapy and photobiomodulation protocols in patients with COVID-19: A multicenter case series. *Photodiagnosis Photodyn. Ther.* **2022**, *38*, 102743. [CrossRef] [PubMed]
68. Prominent Users of Light Therapy. Available online: https://ledquantumlightacademy.ca/about/prominent-users-of-light-therapy/ (accessed on 4 August 2022).
69. Whittemore, P.B. COVID-19 fatalities, latitude, sunlight, and vitamin D. *Am. J. Infect. Control* **2020**, *48*, 1042–1044. [CrossRef] [PubMed]
70. Ratnesar-Shumate, S.; Williams, G.; Green, B.; Krause, M.; Holland, B.; Wood, S.; Bohannon, J.; Boydston, J.; Freeburger, D.; Hooper, I.; et al. Simulated Sunlight Rapidly Inactivates SARS-CoV-2 on Surfaces. *J. Infect. Dis.* **2020**, *222*, 214–222. [CrossRef] [PubMed]
71. Sharun, K.; Tiwari, R.; Dhama, K. COVID-19 and sunlight: Impact on SARS-CoV-2 transmissibility, morbidity, and mortality. *Ann. Med. Surg.* **2021**, *66*, 102419. [CrossRef] [PubMed]
72. Guasp, M.; Laredo, C.; Urra, X. Higher solar irradiance is associated with a lower incidence of coronavirus disease 2019. *Clin. Infect. Dis.* **2020**, *71*, 2269–2271. [CrossRef]
73. Fernandes, A.B.; de Lima, C.J.; Villaverde, A.; Pereira, P.C.; Carvalho, H.C.; Zângaro, R.A. Photobiomodulation: Shining Light on COVID-19. *Photobiomodul. Photomed. Laser Surg.* **2020**, *38*, 395–397. [CrossRef]
74. Nejatifard, M.; Asefi, S.; Jamali, R.; Hamblin, M.R.; Fekrazad, R. Probable positive effects of the photobiomodulation as an adjunctive treatment in COVID-19: A systematic review. *Cytokine* **2021**, *137*, 155312. [CrossRef]
75. Bumah, V.V.; Masson-Meyers, D.S.; Enwemeka, C.S. Pulsed 450 nm blue light suppresses MRSA and Propionibacterium acnes in planktonic cultures and bacterial biofilms. *J. Photochem. Photobiol. B* **2020**, *202*, 111702. [CrossRef]
76. Bumah, V.V.; Morrow, B.N.; Cortez, P.M.; Bowman, C.R.; Rojas, P.; Masson-Meyers, D.S.; Suprapto, J.; Tong, W.G.; Enwemeka, C.S. The importance of porphyrins in blue light suppression of Streptococcus agalactiae. *J. Photochem. Photobiol. B* **2020**, *212*, 111996. [CrossRef]
77. Enwemeka, C.S.; Bumah, V.V.; Mokili, J.L. Pulsed blue light inactivates two strains of human coronavirus. *J. Photochem. Photobiol. B* **2021**, *222*, 112282. [CrossRef]

78. Enwemeka, C.S.; Bumah, V.V.; Castel, J.C.; Suess, S.L. Pulsed blue light, saliva and curcumin significantly inactivate human coronavirus. *J. Photochem. Photobiol. B* **2022**, *227*, 112378. [CrossRef] [PubMed]
79. Brochetti, R.A.; Leal, M.P.; Rodrigues, R.; da Palma, R.K.; de Oliveira, L.; Horliana, A.; Damazo, A.S.; de Oliveira, A.; Vieira, R.P.; Lino-Dos-Santos-Franco, A. Photobiomodulation therapy improves both inflammatory and fibrotic parameters in experimental model of lung fibrosis in mice. *Lasers Med. Sci.* **2017**, *32*, 1825–1834. [CrossRef]
80. Enwemeka, C.S.; Bumah, V.V.; Masson-Meyers, D.S. Light as a potential treatment for pandemic coronavirus infections: A perspective. *J. Photochem. Photobiol. B* **2020**, *207*, 111891. [CrossRef]
81. De Santis, R.; Luca, V.; Näslund, J.; Ehmann, R.K.; De Angelis, M.; Lundmark, E.; Nencioni, L.; Faggioni, G.; Fillo, S.; Amatore, D.; et al. Rapid inactivation of SARS-CoV-2 with LED irradiation of visible spectrum wavelengths. *J. Photochem. Photobiol.* **2021**, *8*, 100082. [CrossRef]
82. Liebert, A.; Bicknell, B.; Markman, W.; Kiat, H. A Potential Role for Photobiomodulation Therapy in Disease Treatment and Prevention in the Era of COVID-19. *Aging Dis.* **2020**, *11*, 1352–1362. [CrossRef]
83. Salehpour, F.; Hamblin, M.R. Photobiomodulation for Parkinson's Disease in Animal Models: A Systematic Review. *Biomolecules* **2020**, *10*, 610. [CrossRef]
84. Montazeri, K.; Farhadi, M.; Fekrazad, R.; Akbarnejad, Z.; Chaibakhsh, S.; Mahmoudian, S. Transcranial photobiomodulation in the management of brain disorders. *J. Photochem. Photobiol. B* **2021**, *221*, 112207. [CrossRef]
85. Belova, A.N.; Israelyan, Y.A.; Sushin, V.O.; Shabanova, M.A.; Rezenova, A.M. Transkranial'naya fotobiomodulyatsiya v terapii neirodegenerativnykh zabolevanii golovnogo mozga: Teoreticheskie predposylki i klinicheskaya effektivnost' [Transcranial photobiomodulation in therapy of neurodegenerative diseases of the brain: Theoretical background and clinical effectiveness]. *Vopr. Kurortol. Fizioter. Lech. Fiz Kult.* **2021**, *98*, 61–67. [CrossRef]
86. Liebert, A.; Bicknell, B.; Laakso, E.L.; Jalilitabaei, P.; Tilley, S.; Kiat, H.; Mitrofanis, J. Remote Photobiomodulation Treatment for the Clinical Signs of Parkinson's Disease: A Case Series Conducted During COVID-19. *Photobiomodul. Photomed. Laser Surg.* **2022**, *40*, 112–122. [CrossRef]
87. Amaroli, A.; Ravera, S.; Zekiy, A.; Benedicenti, S.; Pasquale, C. A Narrative Review on Oral and Periodontal Bacteria Microbiota Photobiomodulation, through Visible and Near-Infrared Light: From the Origins to Modern Therapies. *Int. J. Mol. Sci.* **2022**, *23*, 1372. [CrossRef]
88. Ailioaie, L.M.; Litscher, G. Probiotics, Photobiomodulation, and Disease Management: Controversies and Challenges. *Int. J. Mol. Sci.* **2021**, *22*, 4942. [CrossRef]
89. Woodruff, L.D.; Bounkeo, J.M.; Brannon, W.M.; Dawes, K.S.; Barham, C.D.; Waddell, D.L.; Enwemeka, C.S. The efficacy of laser therapy in wound repair: A meta-analysis of the literature. *Photomed. Laser Surg.* **2004**, *22*, 241–247. [CrossRef]
90. Bjordal, J.M.; Lopes-Martins, R.A.B.; Joensen, J.; Iversen, V.V. The anti-inflammatory mechanism of low level laser therapy and its relevance for clinical use in physiotherapy. *Phys. Ther. Rev.* **2010**, *15*, 286–293. [CrossRef]
91. Tumilty, S.; Munn, J.; McDonough, S.; Hurley, D.A.; Basford, J.R.; Baxter, G.D. Low level laser treatment of tendinopathy: A systematic review with meta-analysis. *Photomed. Laser Surg.* **2010**, *28*, 3–16. [CrossRef]
92. Jang, H.; Lee, H. Meta-analysis of pain relief effects by laser irradiation on joint areas. *Photomed. Laser Surg.* **2012**, *30*, 405–417. [CrossRef]
93. Barger, B.K.; Bisges, A.M.; Fox, D.B.; Torres, B. Low-Level Laser Therapy for Osteoarthritis Treatment in Dogs at Missouri Veterinary Practice. *J. Am. Anim. Hosp. Assoc.* **2020**, *56*, 139–145. [CrossRef]
94. Barale, L.; Monticelli, P.; Raviola, M.; Adami, C. Preliminary clinical experience of low-level laser therapy for the treatment of canine osteoarthritis-associated pain: A retrospective investigation on 17 dogs. *Open Vet. J.* **2020**, *10*, 116–119. [CrossRef]
95. Mokmeli, S.; Vetrici, M. Low level laser therapy as a modality to attenuate cytokine storm at multiple levels, enhance recovery, and reduce the use of ventilators in COVID-19. *Can. J. Respir. Ther.* **2020**, *56*, 25–31. [CrossRef]
96. de Matos, B.T.L.; Buchaim, D.V.; Pomini, K.T.; Barbalho, S.M.; Guiguer, E.L.; Reis, C.H.B.; Bueno, C.R.d.S.; Cunha, M.R.d.; Pereira, E.d.S.B.M.; Buchaim, R.L. Photobiomodulation Therapy as a Possible New Approach in COVID-19: A Systematic Review. *Life* **2021**, *11*, 580. [CrossRef]
97. Hamblin, M.R. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. *AIMS Biophys.* **2017**, *4*, 337–361. [CrossRef]
98. Kitchen, L.C.; Berman, M.; Halper, J.; Chazot, P. Rationale for 1068 nm Photobiomodulation Therapy (PBMT) as a Novel, Non-Invasive Treatment for COVID-19 and Other Coronaviruses: Roles of NO and Hsp70. *Int. J. Mol. Sci.* **2022**, *23*, 5221. [CrossRef]
99. Soheilifar, S.; Fathi, H.; Naghdi, N. Photobiomodulation therapy as a high potential treatment modality for COVID-19. *Lasers Med. Sci.* **2021**, *36*, 935–938. [CrossRef]
100. Sherafat, S.J.; Mokmeli, S.; Rostami-Nejad, M.; Razaghi, Z.; Tavirani, M.R.; Razzaghi, M. The Effectiveness of Photobiomudulation Therapy (PBMT) in COVID-19 Infection. *J. Lasers Med. Sci.* **2020**, *11*, S23–S29. [CrossRef]
101. Hanna, R.; Dalvi, S.; Sălăgean, T.; Pop, I.D.; Bordea, I.R.; Benedicenti, S. Understanding COVID-19 Pandemic: Molecular Mechanisms and Potential Therapeutic Strategies. An Evidence-Based Review. *J. Inflamm. Res.* **2021**, *14*, 13–56. [CrossRef]
102. Chang, Y.L.; Chang, S.T. The effects of intravascular photobiomodulation on sleep disturbance caused by Guillain-Barré syndrome after Astrazeneca vaccine inoculation: Case report and literature review. *Medicine* **2022**, *101*, e28758. [CrossRef]

103. Arnabat-Dominguez, J.; Vecchio, A.D.; Todea, C.; Grzech-Leśniak, K.; Vescovi, P.; Romeo, U.; Nammour, S. Laser dentistry in daily practice during the COVID-19 pandemic: Benefits, risks and recommendations for safe treatments. *Adv. Clin. Exp. Med.* **2021**, *30*, 119–125. [CrossRef] [PubMed]
104. Pacheco, J.A.; Molena, K.F.; Martins, C.; Corona, S.; Borsatto, M.C. Photobiomodulation (PBMT) and antimicrobial photodynamic therapy (aPDT) in oral manifestations of patients infected by Sars-CoV-2: Systematic review and meta-analysis. *Bull. Natl Res. Cent.* **2022**, *46*, 140. [CrossRef]
105. Weber, H.M.; Mehran, Y.Z.; Orthaber, A.; Saadat, H.H.; Weber, R.; Wojcik, M. Successful Reduction of SARS-CoV-2 Viral Load by Photodynamic Therapy (PDT) Verified by QPCR—A Novel Approach in Treating Patients in Early Infection Stages. *Med. Clin. Res.* **2020**, *5*, 311–325.
106. Liebert, A.; Bicknell, B.; Laakso, E.L.; Heller, G.; Jalilitabaei, P.; Tilley, S.; Mitrofanis, J.; Kiat, H. Improvements in clinical signs of Parkinson's disease using photobiomodulation: A prospective proof-of-concept study. *BMC Neurol.* **2021**, *21*, 256. [CrossRef] [PubMed]
107. Morimoto, S.; Rosin, J.; Matuck, B.F.; Schröter, G.; Rodrigues, M.; Ramalho, K.M.; Raggio, D.P.; Moreira, M.S.; da Silva, L. aPDT for oral decontamination of hospitalized patients with COVID 19. *Photodiagnosis Photodyn. Ther.* **2022**, *38*, 102762, Erratum in *Photodiagnosis Photodyn. Ther.* **2022**, *38*, 102824. [CrossRef]
108. Besegato, J.F.; de Melo, P.; Tamae, P.E.; Alves, A.; Rondón, L.F.; Leanse, L.G.; Dos Anjos, C.; Casarin, H.H.; Chinelatti, M.A.; Faria, G.; et al. How can biophotonics help dentistry to avoid or minimize cross infection by SARS-CoV-2? *Photodiagnosis Photodyn. Ther.* **2022**, *37*, 102682. [CrossRef]