30 Photobiomodulation and Antiviral Photodynamic Therapy in COVID-19 Management

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Abstract

Coronavirus disease 2019 (COVID-19) has shocked the world by its spread and contagiousness. There is no approved vaccine and no proven treatment for this infection. Some potential treatments that have already been associated with antiviral and anti-inflammatory effects are under investigation. Photobiomodulation therapy (PBMT) is a photon-based therapy that uses light to mediate a variety of metabolic, analgesic, anti-inflammatory, and immunomodulatory effects. Antiviral photodynamic therapy (aPDT) is a branch of photodynamic therapy based on the reaction between a photosensitizing agent and a light source in the presence of oxygen, which can produce oxidative and free radical agents to damage the viral structures such as proteins and nucleic acids. This chapter aims to discuss

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the potential therapeutic benefit of PBMT and aPDT in the context of the novel coronavirus. Studies indicate that PBMT and aPDT could be useful in many viral and bacterial pulmonary complications like influenza, SARS-CoV, and MERS, but we found no direct study on SARS-CoV-2. With a combination of PBMT and aPDT, we may be able to combat COVID-19 with minimal interference with pharmaceutical agents. It might improve the efficacy of PBMT and aPDT by using monoclonal antibodies and preparing new photosensitizers at the nanoscale that target the lung tissue specifically. More animal and human studies would need to take place to reach an effective protocol. This chapter would encourage other scientists to work on this new platform.

Keywords

Antiviral photodynamic therapy · COVID-19 · Low-level laser therapy · Photobiomodulation · Photodynamic therapy

30.1 Introduction

In late 2019, several patients presenting with symptoms of pneumonia without any identified cause were reported in Wuhan, Hubei Province, China (Li et al. 2020). After analysis of the sequence of development and possible exposure, the new disease was determined to be caused by a new coronavirus (CoV) named 2019-nCoV (Zhu et al. 2020). Subsequently, the World Health Organization (WHO) announced the nomenclature of Coronavirus Disease-2019 (COVID-19), for this novel coronavirus pneumonia-related disease on February 11, 2020 (WHO 2020). At the same time, the International Committee on Taxonomy of Viruses (ICTV) introduced the new coronavirus as SARS-CoV-2 (Gorbalenya et al. 2020).

30.2 Virology

30.2.1 Origin, Classification, and Genetical Features

Clinicians diagnosed the disease as a pneumonia-related infection caused by a virus based on clinical manifestations, chest radiographs, and blood tests. First epidemiological studies concluded that most of the suspected cases had been exposed to a local Huanan Seafood Market. Scientists first suggested that the origin of the outbreak was the market because SARS-CoV-2 had been isolated in environmental samples. However, this conclusion was disputed because the earliest/first case had no reported link to the mentioned market (Huang et al. 2020). Furthermore, at least two different strains of SARS-CoV-2 had been identified a few months earlier before COVID-19 was officially reported (Xiong et al. 2020). At present, the precise origin of SARS-CoV-2 remains unknown.

SARS-CoV-2 was first isolated from the bronchoalveolar lavage fluid (BALF) of three COVID-19 patients in Wuhan Jinyintan Hospital on December 30, 2019 (Zhu et al. 2020). Sequencing and evolutionary tree analysis showed that SARS-CoV-2 is a member of the CoV family (Zhu et al. 2020; Zhou et al. 2020). Coronaviruses are enveloped positive-sense single-stranded RNA viruses. These viruses are associated with respiratory, enteric, hepatic, and neurologic diseases (Weiss and Leibowitz 2011; De Wilde et al. 2018), and both SARS coronavirus (SARS-CoV) and MERS coronavirus (MERS-CoV) are members of CoVs (Weiss and Leibowitz 2011). Genetic studies indicate that SARS-CoV-2 shares 79.5% and 50% sequence identity to SARS-CoV and MERS-CoV, respectively, and belongs to the B (*Sarbecovirus*) of CoVs (Zhu et al. 2020; Zhou et al. 2020; Lu et al. 2020; Wu et al. 2020). Like other CoVs, the SARS-CoV-2 virion has a nucleocapsid composed of genomic RNA and phosphorylated nucleocapsid (N) protein. It has two types of spike proteins: the spike glycoprotein trimer (S)

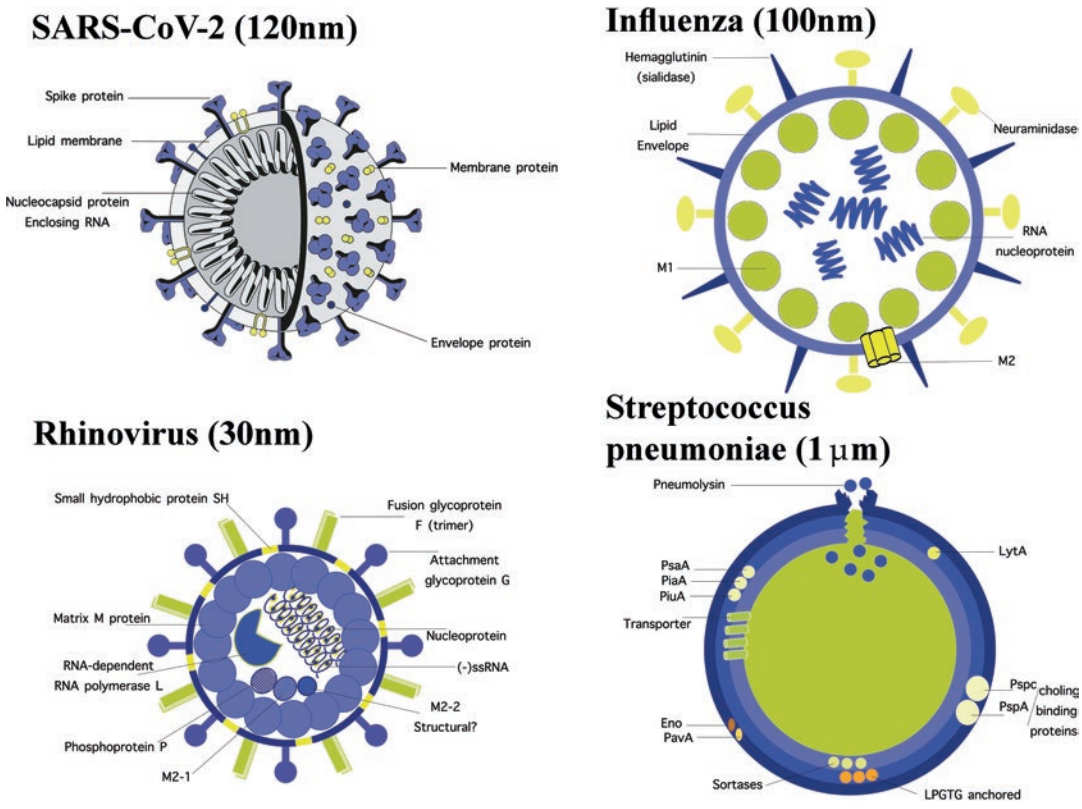


Fig. 30.1 Structural comparison between SARS-Cov-2, influenza, rhinovirus, and *Streptococcus pneumoniae*

and the hemagglutinin-esterase (HE). The former is common to all CoVs, while the latter is shared among certain CoVs. The envelope (E) protein and the membrane (M) protein are among the S proteins in the viral envelope (Wu et al. 2020). Figure 30.1 shows SARs-CoV-2 and some similar viruses and bacteria.

30.2.2 Receptor Interactions and Cell Entry

Human angiotensin-converting enzyme 2 (ACE2) is the receptor that the SARS-CoV-2 uses to enter cells just like SARS-CoV (Zhou et al. 2020; Li et al. 2003). This receptor is a membrane receptor found in the lung, heart, kidney, and intestine and has been associated with cardiovascular diseases. ACE2 possesses a direct binding site for the S proteins of CoVs (Donoghue et al. 2000). The S protein undergoes a structural rearrangement to fuse the viral membrane and the host cell (De Wilde et al. 2018). The S1 subunit triggers this process, which leads to the transition of the S2 subunit to a highly stable post-fusion conformation (De Wilde et al. 2018).

30.3 Epidemiology

30.3.1 Source of Infection

Patients are the primary source of infection, especially those presenting with severe infection and symptoms. Other potential sources of infection are asymptomatic persons or patients who are still within the incubation period and have no signs or symptoms of respiratory infection. These patients help virus shedding (Hoehl et al. 2020). Moreover, it is the first time in the history of human infectious diseases that samples from recovered COVID-19 patients continue to present a positive RT-PCR test (Lan et al. 2020).

30.3.2 Routes of Transmission

Respiratory droplets and contact transition are the main transition routes. Recent reports implied a fecal-oral risk of transition as well (Commission 2020). Virus-contaminated foods are yet to be recognized as a source of infection and transition. Besides, the possibility of mother to baby transmission of SARS-CoV-2 during pregnancy or childbirth is unknown.

30.3.3 High-Risk Population

Age, obesity, smoking as well as underlying disorders such as asthma, diabetes, cardiovascular diseases, and cancer increase the risk and susceptibility to SARS-CoV-2. Additionally, people in close contact with infectious sources, including healthcare workers and family members of infected patients, are the high-risk population (Jin et al. 2020b).

30.3.4 Spectrum of Infection

COVID-19 is considered to be a self-limiting infectious disease, and patients mostly suffer from mild symptoms and recover in 1–2 weeks. SARS-CoV-2 outcomes range from asymptomatic infection (1.2%) and mild to moderate infection (80.9%) to severe infection (13.8%), critical infection (4.7%), and death (2.3%) (Jin et al. 2020b). Figure 30.2 shows the confirmed cases and total deaths related to COVID-19.

30.4 Diagnosis

30.4.1 Nucleic Acid Test

Shortly after the initial outbreak, viral sequence detection diagnostic tests using reverse transcription-polymerase chain reaction (RT-PCR) or next-generation sequencing platforms became available. False negatives remain a problem when using nucleic acid tests. As a solution to the low detection efficiency, improved types of rapid viral nucleic acid diagnostic tests have been invented, especially a nucleic acid paper test, which has made naked-eye detection of SARS-CoV-2 possible within 3 min (Jin et al. 2020b).

30.4.2 Serologic Diagnosis

Studies show that SARS-CoV-2 patients have acute serological responses (Zhou 2020). Immunochromatography, colloidal gold, and other relevant detection methods for serum antibodies became available in a short time (Jin et al. 2020b).

30.4.3 Chest Radiography or Computed Tomography (CT) Scan

It is an important tool for COVID-19 diagnosis in clinical practice. Most COVID-19 patients display similar features on CT Scan images, such as signs of bilateral distribution of patchy shadows and ground-glass opacity (Kanne 2020).

30.5 Pathogenesis

30.5.1 Virus Entry and Spread

SARS-CoV-2 is transmitted via respiratory droplets, contact, and possibly through fecal-oral transmission (Jin et al. 2020b). The mucosal epithelium of the upper respiratory tract (nasal cavity and pharynx) is the place in which the virus is presumed first to enter and replicated. On the other hand, further virus replication takes place in the lower respiratory tract and gastrointestinal mucosa (Xiao et al. 2020), causing a mild viremia. Asymptomatic cases are controlled in this stage. Non-respiratory symptoms were also seen in some patients, such as the acute liver and heart injury, kidney failure, and diarrhea (Wang et al. 2020; Jin et al. 2020b), suggesting multiple organ

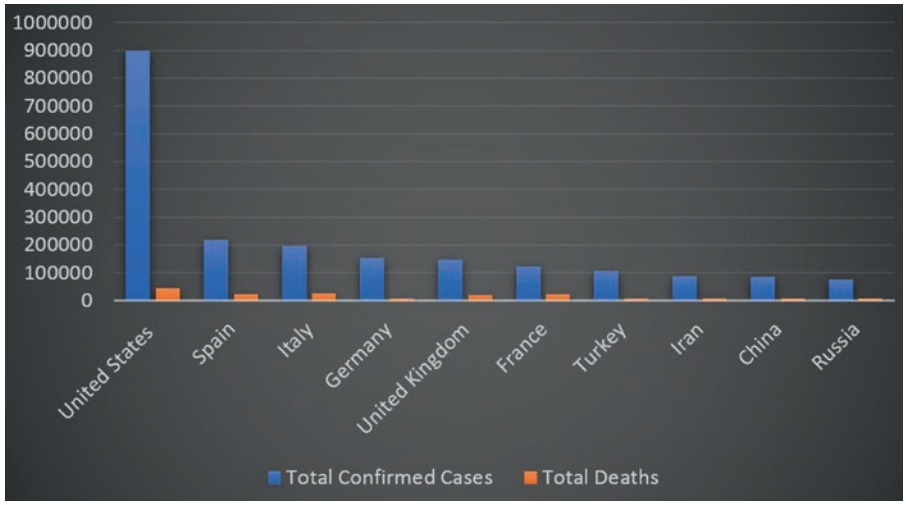


Fig. 30.2 Top ten countries with reported laboratory-confirmed COVID-19 cases and death as of 25 April 2020 (WHO 2020)

involvement. ACE2 is expressed in the nasal mucosa, bronchus, lung, heart, esophagus, kidney, stomach, bladder, and ileum, so all these organs are vulnerable to SARS-CoV-2 infection (Zou et al. 2020). In recent studies, scientists have suggested the potential pathogenicity of the SARS-CoV-2 in testicular tissues raising the concern of fertility effects in younger patients (Fan et al. 2020).

30.5.2 Pathological Findings

The first report (Xu et al. 2020) of pathological findings in a severe COVID-19 patient showed bilateral diffuse alveolar damage (DAD) with cellular fibromyxoid exudates. Tissue from the left lung displayed pulmonary edema with hyaline membrane formation suggesting an early phase of acute respiratory distress syndrome (ARDS). The right lung, on the other hand, demonstrated the desquamation of pneumocytes and hyaline membrane formation, indicating acute respiratory distress syndrome. Both lungs showed interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes. Viral cytopathic-like changes also occur in intra-alveolar spaces. All these pulmonary pathological findings are similar to those of SARS (Ding et al. 2003) and MERS (De Wilde et al. 2018). On the other hand, massive mucus secretion was found in the lungs of patients who died from COVID-19, which is different from SARS and MERS (Jin et al. 2020b).

30.6 Clinical Features

In the first 41 patients (Huang et al. 2020), the most common symptoms were fever (98%), cough (76%), and myalgia or fatigue (44%). Additional symptoms were sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%). Moreover, more than 50% of patients experienced dyspnea. Blood tests showed average or reduced (25%) white blood cell count and lymphopenia (65%) (Huang et al. 2020). Bilateral involvement of the lungs was seen in 98% of patients, as demonstrated in thoracic CT. ICU patients mostly display bilateral multiple lobular involvements and subsegmental areas of consolidation, while non-ICU patients show bilateral ground-glass opacity and subsegmental areas of consolidation (Zhu et al. 2020; Huang et al. 2020).

30.6.1 Acute Respiratory Distress Syndrome (ARDS)

ARDS is a fatal lung condition in which sufficient oxygen is prevented from reaching the lungs and hence the circulation. It is responsible for most deaths in respiratory disorders and acute lung injury (Thompson et al. 2017). Clinically, fatal cases of human SARS-CoV, MERS-CoV, and SARS-CoV-2 infections exhibit severe respiratory distress requiring mechanical ventilation, while the histopathology findings also support ARDS (Xu et al. 2020; Ding et al. 2003; Ng et al. 2016). Based on previous studies, the occurrence of ARDS is closely connected to genetic features and inflammatory findings. There are more than 40 candidate genes related to the development of ARDS and its consequences (Meyer et al. 2013). These genes mainly involve molecular pathways of ACE2 and cytokines (e.g., IL-10, interleukin 10; TNF, tumor necrosis factor (TNF); and VEGF, vascular endothelial growth factor). Different outcomes of ARDS are considered to be associated with increased levels of plasma IL-6 and IL-8 (Thompson et al. 2017). These biomarkers suggest both an inflammatory explanation and possible treatment for ARDS following SARS-CoV-2 infection.

30.6.2 Cytokine Storm Phenomenon

The leading cause of fatality is likely to be uncontrolled pulmonary inflammation, which has been shown to be caused by extreme inflammatory responses during SARS-CoV-2 infection. The result of a recent study concluded that rapid viral replication and cellular damage, virus-induced ACE2 downregulation and shedding, and antibody-dependent enhancement (ADE) are the causes of aggressive inflammation caused by SARS-CoV-2 (Fu et al. 2020). SARS-CoV-2 and SARS-CoV use the same receptor (ACE2) for cell entry, suggesting the same cells are targeted and infected (Gu et al. 2005). Excessive production of pro-inflammatory cytokines and chemokines is triggered by massive epithelial and endothelial cell death and vascular leakage caused by the initial onset of rapid viral replication (Jin et al. 2020b). Pulmonary loss of ACE2 function is considered to be related to acute lung injury (Imai et al. 2008) because it leads to dysfunction of the renin-angiotensin system (RAS), which worsens the inflammation and causes vascular permeability. ADE is a well-known phenomenon in virology, and it has been confirmed in multiple viral infections (Takada 2003). ADE can induce viral cellular uptake of the virus-antibody complexes resulting in enhanced infection of target cells (Takada and Kawaoka 2003).

30.6.3 Cellular Immune Dysfunction

In patients with severe COVID disease, peripheral CD4+ and CD8+ T cells are reduced in counts, but their activity is increased, as indicated by an abundance of cytotoxic granules, including CD8+ T cells and CD4+ T cells (Xu et al. 2020).

30.7 Potential Therapeutics

There is no specific treatment or vaccine for COVID-19, and, still, systematic treatment strategies are recommended for clinical practice (Jin et al. 2020a). Potential therapeutic strategies currently available for the treatment of SARS-CoV-2 are listed below (Mahase 2020).

30.7.1 Chloroquine

It is an approved treatment for malaria and rheumatoid arthritis. It has been tested against SARS-CoV-2 and has been suggested to be highly effective, but the evidence is limited and contradictory. Chloroquine can interfere with viral cell entry by changing the acidity of the endocytosis compartment and inhibition of initial viral replication. Chloroquine may also change the ability of the virus to bind to the outside of the host cell. Finally, this drug has various effects on immune cells, which has made it a possible treatment for

autoimmune conditions like lupus and rheumatoid arthritis. However, the side effects of chloroquine, when used in conjunction with additional drugs, do not render it a safe treatment compound.

30.7.2 Kaletra

Kaletra (lopinavir/ritonavir) is usually used to treat HIV. The combination of Kaletra and other antiviral drugs has been tested against SARS. Lopinavir is an inhibitor of HIV protease, which prevents cleavage of the Gag-Pol polyprotein, resulting in the production of immature, noninfectious viral particles. As co-formulated in Kaletra, ritonavir can inhibit the CYP3A-mediated metabolism of lopinavir, thereby providing increased plasma levels of lopinavir.

30.7.3 Interferon

SNG001 is an inhaled form of interferon β, which is a part of the lung's defense system against viruses. It is believed that SNG001 can increase the production of INF-β, which is considered to be suppressed by coronaviruses. This phenomenon could prevent or decrease symptoms of severe respiratory illness, such as pneumonia.

30.7.4 Remdesivir

It is going through clinical trials for potential COVID-19 treatment as a virus replication inhibitor. Wang et al. found that this drug alone cannot provide significant clinical or antiviral effects in severely ill patients with COVID-19. Further studies with larger sample sizes are necessary for a better understanding of this drug's effects. Furthermore, different strategies to improve the antiviral potency of this drug, such as higher dose regimens and combination with antivirals and immunosuppressants targeting pro-inflammatory cytokines, such as IL-6, IL-1, or TNF-α, need to be done (Wang et al. 2020).

30.7.5 Tocilizumab (Actemra)

It is a monoclonal antibody used for rheumatoid arthritis treatment. It blocks the IL-6 signaling pathway.

30.7.6 hrsACE2 (Human Recombinant Soluble Angiotensin-Converting Enzyme 2)

It is a genetically modified type of ACE2 which could significantly prevent SARS-CoV-2 entry (Monteil et al. 2020).

30.7.7 Immunoglobulin Therapy

Convalescent plasma or hyperimmune immunoglobulins may help with both the removal of free virus and infected cell immune clearance (Sanders et al. 2020). All these treatments can be seen in Fig. 30.3. In conclusion, most current treatment regimens are focused on antiviral and anti-inflammatory effects, stifling the cytokine storm and increasing tissue oxygenation.

30.8 Photobiomodulation Therapy

Photobiomodulation therapy refers to the interaction between visible light (usually red) or near-infrared light with low energy density and biological tissue that does not induce thermal effects (tissue temperature does not rise above 98 F). Light sources in PBM can be laser or light-emitting diode (LED) systems that can emit wavelengths between 600 nm–1200 nm with energy densities of 1–20 J/cm^2. Due to their low energy density, this type of irradiation can treat various injuries or pathologies without causing thermal damage in the target tissue (Migliorati et al. 2013; Theocharidou et al. 2017; Huang et al. 2011).

Biomodulation effects of PBMT occur with the interaction of light with photoacceptors,

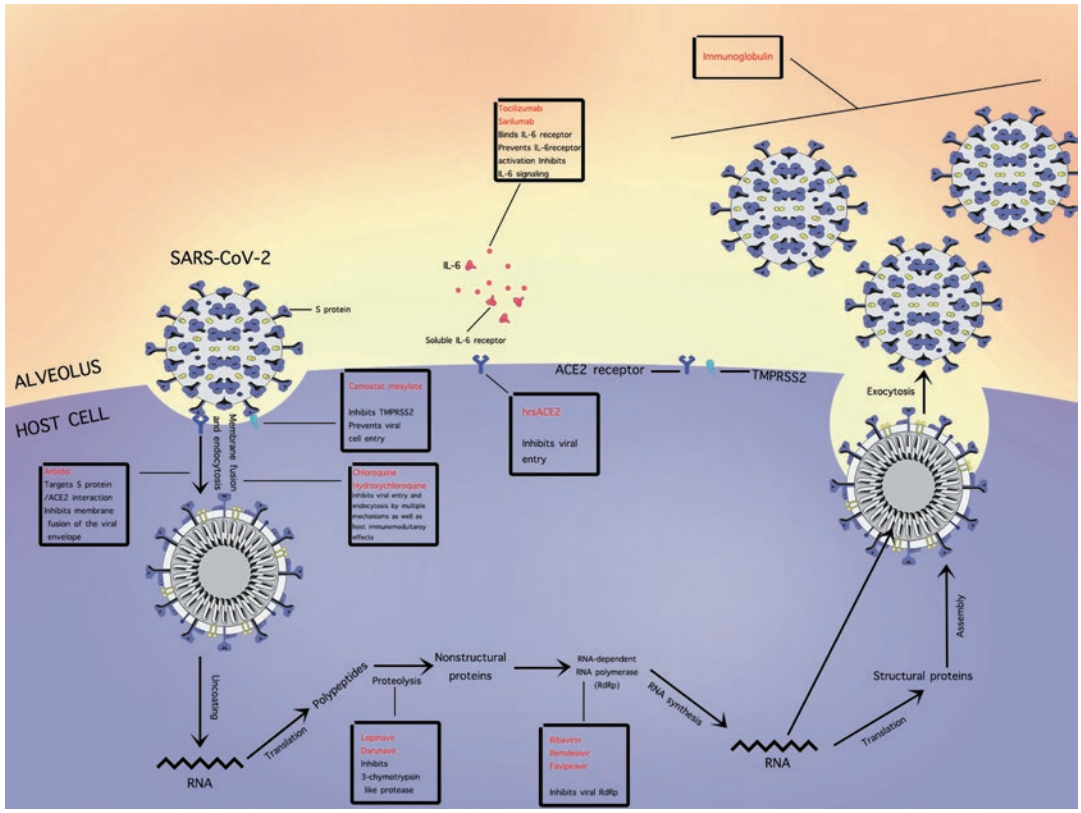


Fig. 30.3 Current SARS-CoV-2 treatment modalities

resulting in mitochondrial signaling events that mediate photophysical, photochemical, and photobiological effects in tissue (Migliorati et al. 2013; Theocharidou et al. 2017). Photochemical reactions can be caused by the effect of visible light or NIR (near-infrared) on mitochondrial photoacceptors and the process of ATP synthesis. The effects of light radiation on Ca ++ channels in cell membranes is another basis for photophysical reactions (Huang et al. 2011; Karu 1989b; Smith 1991; Lopes et al. 2009, 2010; Heidari et al. 2017).

Given the importance of mitochondria in energy production and cellular metabolism, recent studies have paid particular attention to their role in the mechanism of action of PBM (Fig. 30.4). The first PBMT mechanism at the cellular level occurs by the absorption of monochromatic visible and NIR by cellular respiratory chain components. Absorption of R-NIR radiations by mitochondrial photoacceptors activates the respiratory chain, NADH dehydrogenase, cytochrome C reductase, and oxidase, as well as ATP synthase (Karu 2008; Karu and Kolyakov 2005). Accordingly, cytochrome c oxidase (Cco) can be considered the primary photoacceptor that absorbs R-NIR radiations in mammalian cells (Karu 1989a; Huang et al. 2011; Karu and Kolyakov 2005).

The absorption of light by the components of the respiratory chain causes the short-term activation of the respiratory chain and the oxidation of the NADH pool. This stimulation of oxidative phosphorylation leads to changes in mitochondrial redox status as well as cell cytoplasm. The electron transfer chain can provide increased levels of energy to the cell by increasing ATP production, as well as increasing the electrical potential of the mitochondrial membrane, alkalizing the cytoplasm, and activating the synthesis

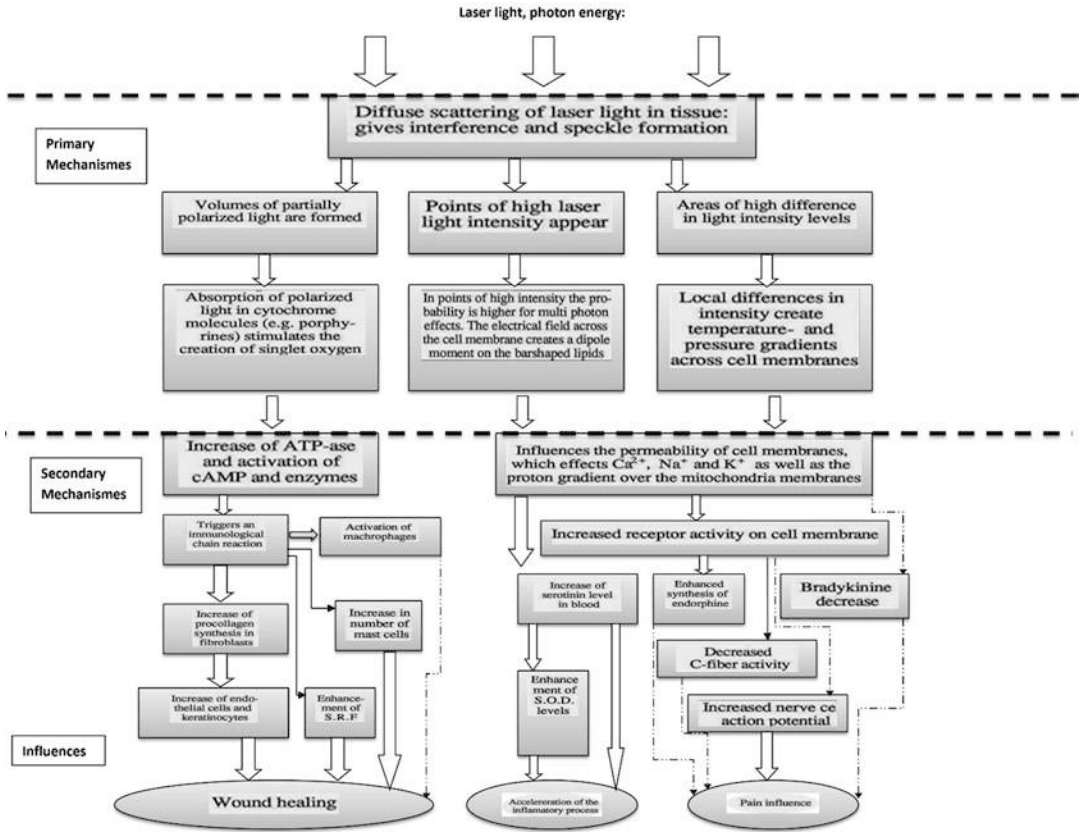


Fig. 30.4 Mechanisms of photobiomodulation

of nucleic acids. Also, infrared radiation transmits biological messages by activating ion channels and affecting the permeability of cell membranes as well as the concentration of Na + -K + flux and Ca + 2 ions (Smith 1991). Because ATP is a common form of energy for the cell, PBMT has the potential to stimulate normal cell functions. By increasing cellular respiratory metabolism, PBMT can also affect the cellular electrical-physiological characteristics (Moslemi et al. 2014; Hamblin and Demidova 2006). Further stimulation of cell proliferation and inhibition of cell death, as well as the effect on the production of extracellular matrix proteins, are among the most critical effects of PBMT on the expression of genes (Theocharidou et al. 2017).

In general, PBMT can be used in both direct and indirect ways. For example, in the transthoracic method, the lung tissue is exposed to direct infrared lasers with wavelengths of 810 nm or 940–970 nm. Intravenous radiation is also a type of direct radiation that can play an important role in the systemic effects of PBMT. The indirect method can be used to irradiate blood cells through the skin adjacent to the blood vessels in the wrist, nasal mucosa, and the back area of the knee, or even sublingual tissues, which is called the transcutaneous technique (Fekrazad 2020).

Among the most important clinical applications of PBMT are accelerating the healing process of the skin or mucosal wounds; reducing acute and chronic pain; regulating the function of the immune system, especially in people with immunodeficiency, anti-inflammatory function by regulating levels of pro-inflammatory cytokines, as well as oxygenation of damaged tissue; and helping tissue regeneration by stimulating stem cell proliferation and differentiation (Fig. 30.4) (Desmet et al. 2006; Chiari 2016; Fujita et al. 2008; Fekrazad 2020).

30.8.1 PBM and Pro-inflammatory Cytokine

Cytokines are hormone-like soluble proteins or glycoproteins that allow communication between cells and the extracellular environment. When an organ or limb is damaged or infected, an immune response is triggered to suppress the infection, in which the release of pro-inflammatory cytokines indicates the body's attempt to respond to the infection. Several cytokines play a key role in the development of acute inflammatory responses, including IL-1, IL-6, IL-8, IL-11, TNF-α, G-CSF (granulocyte colony-stimulating factor), and GM-CSF (granulocyte-macrophage colony-stimulating factor). Among these, IL-1 and TNF (α and β) have the highest power to induce inflammation (Mahnam and Payab 2016).

Studies have shown that one of the important functions of PBM is to reduce all the markers of immune activation such as MHC class II, CD86, and CD11c in inflammatory cells. Also, the IL-12 secretion has been another effect of PBM. Hwang et al. stated the decreased expression of IL-8 and IL-6 (two important pro-inflammatory cytokines in macrophages) with PBM. Chen et al. confirmed the vital role of PBM in reducing inflammatory markers (cyclooxygenase-2 (COX2), prostaglandin E2 (PGE2), granulocyte colony-stimulating factor (GCSF), regulated on activated normal T-cell expressed and secreted (RANTES), and CXCL11) (Chen et al. 2011; Hwang et al. 2015). Yamaura et al. also used PBM (810 nm, 5 or 25 J/cm2) to confirm its role in reducing levels of TNF-α and interleukins (IL)-1beta, and IL-8 (Yamaura et al. 2009).

30.8.2 PBM on Macrophage Phenotype

Another important effect of PBM at the cellular level is its role in altering the phenotype of monocyte or macrophage cells. Monocytes and macrophages critically contribute to innate immunity. These cells detect dangerous and invasive pathogens in the blood and tissues and exert a strong inflammatory immune response that eventually leads to the removal of the pathogens and the establishment of homeostasis in the body. Activated macrophages are differentiated into two different phenotypes, classical macrophages (M1) and alternative macrophages (M2). These phenotypes differ in terms of cytokines, chemokines, ligand receptors, and function. M1 macrophages produce large amounts of lymphokines and are associated with the expression of genes such as IFNγ, TNF-β, and TNF-α. The M2 phenotype shows high production of TGFβ, and IL-10, and exerts anti-inflammatory effects that induce tolerance, immune regulation, and tissue repair. Also, both types of macrophage (M1 and M2 phenotypes) are present in different organs, such as microglia in the brain, alveolar macrophages in the lung, and Kupffer cells in the liver, and are specific to that organ (Hamblin 2017; Jalili et al. 2015).

Fernandes et al. were among the first researchers who found the effect of PBM on reducing TNF-α, COX-2, and iNOS expression in M1 cells. Also, in another study, PBM had a significant effect on reducing CCL3 gene expression in M1 cells. Increased cAMP and decreased TNF-α mRNA are other identified effects following the effect of PBM on alveolar macrophages (Hamblin 2017; Fernandes et al. 2015; Sousa et al. 2017) (Fig. 30.4).

30.8.3 Role of Photobiomodulation in COVID-19 Management

There is not yet any definitive treatment for COVID-19 disease. The main recommended approaches for COVID-19 management are increasing tissue oxygenation, facilitating damaged tissue repair, eliminating the virus, and reducing inflammation. Every treatment, which can promote regeneration of respiratory or other impaired tissues, can be helpful in controlling COVID-19 progression. These may include directly targeted organ or indirect methods as influencing blood flow or oxygenation to damaged tissues. So clinicians usually alleviate symptoms, especially by decreasing inflammation.

One of the innovative approaches is photobiomodulation therapy. Light or low-level lasers irradiate the tissues, and internal or external photoacceptors can absorb the emitted energy. In this noninvasive method, free radicals are produced after light irradiation, which leads to biostimulatory cascades in cellular processes to promote cell proliferation, differentiation, or decrease inflammation (Fekrazad 2020; Tuner and Hode 2004; Khorsandi et al. 2020).

When photoacceptors absorb light or laser, free radicals are produced. Reactive oxygen species (ROS) are of common radicals in this regard. They include singlet oxygen, nitric oxide (NO), or hydrogen peroxide (H_2O_2) (Derr and Fine 1965; Lubart et al. 1990; Mrowiec et al. 1997). They can play the role of secondary messengers at low concentrations, whereas high concentrations can be destructive for cell processes.

Photoacceptors can be divided into internal or external. Internal photoacceptors contain chromophores (like porphyrins) and respiratory chain components in the cell mitochondria, such as NADH oxidase and cytochrome a/a3 (Tuner and Hode 2004; Karu 1996). Photosensitizer drugs are examples of external photoacceptors.

Free radicals can influence cell processes through many mechanisms. Singlet oxygen can promote ATP formation, and ATPs can be used in energy-consuming processes like proliferation or differentiation (Passarella et al. 1984; Hu et al. 2007). Also, low doses of laser irradiation can increase intracellular calcium ions by antiporter process on the cell membrane (Nasu et al. 1989; AlGhamdi et al. 2012) or by increasing the proton-motive force (pmf) in mitochondria (Eduardo et al. 2008) which then affect DNA/RNA synthesis via increasing intracellular pH (alkaline) leading to mitosis and cell proliferation. Also, mitochondrial activation stimulates Na,K-ATPase activity in order to provide more ATP that is necessary for cell division. If the cellular function is impaired (especially by hypoxia), there is more benefit of photobiomodulation compared to situations where the cell functions are intact (Tezel et al. 2009).

Previous studies have shown the benefits of lasers in medical care, including wound healing acceleration, anti-inflammatory effects, and disinfection (Tuner and Hode 2004). One of the advantages of photobiomodulation application is its local effect on the target tissues. General effects of photobiomodulation include metabolic, analgesic, anti-inflammatory, and immunomodulatory functions. The regenerative power of photobiomodulation can increase cellular ability to overcome various problems, such as metabolic and neurological diseases and cardiac or physical rehabilitation. Photobiomodulation is a noninvasive intervention that is local to the target organ and has the least side effects. There have been no adverse systemic effects reported. Based on the reasons mentioned above and the lack of currently available treatment for COVID-19, it is likely that photobiomodulation can be helpful in controlling COVID-19, as an alternative or adjunctive treatment, especially in severe cases with ARDS.

30.8.4 Photobiomodulation of the Lungs

Oliveira et al. designed an in vivo study to evaluate the anti-inflammatory effect of low-level laser therapy on pulmonary and extrapulmonary lipopolysaccharide (LPS)-induced ARDS. They experimentally induced ARDS by intratracheal or intraperitoneal administration of LPS in mice. After 1 h, mice were irradiated by an infrared laser (830 nm wavelength, energy density 3 J/cm^2 per application, power 35mW, continuous mode) in direct contact with the chest skin. They used three points, first at the end part of the trachea, second on the right lung, and third on the left lung. Each irradiation lasted 80 s. 9 J/cm^2 energy was delivered in each application to mice for 240 s. This procedure was repeated three times with a 1 h interval between each application (Oliveira Jr et al. 2014). They found that photobiomodulation could reduce pulmonary inflammation. It was confirmed by a significantly reduced number of total cells and neutrophils in bronchoalveolar lavage (BAL) and neutrophils in the lung parenchyma.

Neutrophil migration to the lungs and secretion of several mediators play important roles in ARDS. These mediators include free radicals, proteases, cytokines, and chemokines (Matute-Bello et al. 2008). The severity and mortality of ARDS have a direct relationship with neutrophil infiltration in the lungs (Fialkow et al. 2006).

Oliveira reported that photobiomodulation could inhibit neutrophil migration to the lungs. They also showed that IL-1 beta, IL-6, IL-8, KC, and TNF-α levels were reduced significantly in BAL fluid and serum after laser irradiation (Oliveira Jr et al. 2014).

IL-1 beta contributes to the initiation of the inflammatory process, and neutrophils are the primary source of IL-1 beta production. It increases the survival rate of neutrophils and is related to the development of ARDS and its poor prognosis. IL-6 is also related to the poor prognosis of ARDS (Meduri et al. 1995; Cho et al. 2012; Rojas et al. 2013; Sharifov et al. 2013) and the prolongation of inflammation (Meduri et al. 1995; Fu et al. 2012). IL-8 stimulates neutrophil chemotaxis and also can increase neutrophil survival in combination with CXCL1/KC. These two functional homologs are related to ARDS severity and morbidity (Meduri et al. 1995; Cho et al. 2012; McGettrick et al. 2006). Therefore, reducing CXCL1/KC by photobiomodulation could be critical in severe ARDS cases. TNF-α affects neutrophil adhesion and activation, and it increases IL-6 generation. TNF-α also induces intravascular coagulation and edema, especially in acute inflammation (Souza et al. 2002; Aimbire et al. 2006).

In one experimental study, Aimbire et al. evaluated Ga-Al-As laser irradiation to reduce airway and lung inflammation induced by gram-negative bacterial LPS in rats (Aimbire et al. 2006). They used a 685 nm wavelength diode laser with 1, 2.5, and 5 J/cm^2 energy densities in continuous mode. They found that 1 and 5 J/cm^2 energy densities were not effective in decreasing rat tracheal hypersensitivity, BAL cellular content, and myeloperoxidase (MPO) activity. Therefore, 2.5 J/cm^2 was selected, the power was 12 mW, the spot size was 0.08 cm^2, the exposure time was 1 min and 20 s, and the irradiation interval was in 90 min, 6, 24, 48 h. Photobiomodulation reduced inflammation in BAL and neutrophil migration to the lungs. PBM also reduced PGE_2 and TXB_2 levels in BAL. PGE_2 has an important role in releasing mediators from mast cells, surveillance and chemotaxis of neutrophils, and mitogenesis (Johnson et al. 1995). TXB_2 mediates inflammation and can stimulate bronchial constriction (Pang and Knox 1997).

De Lima (de Lima et al. 2011a) confirmed the beneficial effects of InGaAlP laser on ARDS induced by LPS in an in vivo study in mice. Laser parameters were 685 nm wavelength, 4.5 J/cm^2 energy density, 17.85 W/cm^2 power density, 35 mW power, 252 s time of irradiation, and 8.82 J energy dose. Irradiation was carried out 15 min after ARDS induction. PBM decreased neutrophil recruitment and TNF production in BAL fluid and also increased cAMP indirectly.

Another study (de Lima et al. 2011b) evaluated the effect of PBM on the acute lung inflammation induced by intestinal ischemia and reperfusion. Diode laser (660 nm, 30 mW, 0.08 cm2 spot size, 5.4 J) was used directly on the rat skin over the right bronchus. Rats were irradiated 1 h after mesenteric artery occlusion. Photobiomodulation reduced inflammation, neutrophil migration, MPO activity, and TNF production. One side effect of laser irradiation was an increase in IL-10. As mentioned before, TNF mediates neutrophil accumulation. IL-10 is associated with a reduction in inflammatory cytokines and the healing of tissue injury. They suggested that acute lung inflammation due to intestinal ischemia may occur with an imbalance between TNF and IL-10 production (de Perrot et al. 2003). So it is promising to promote IL-10 generation and decrease TNF production in order to reduce lung inflammation and subsequent injury.

In addition to TNF-α and IL-1β, another study considered some specific neutrophil chemoattractants (a family of cytokines and neutrophil chemoattractants, CINCs) and macrophage inflammatory protein 2 (MIP-2). Also, CD18 integrin, on polymorphonuclear leukocytes (PMNs), and intracellular adhesion molecules-1 (ICAM-1), on endothelial cells, have important

roles in PMN migration into an inflammatory site (de Lima et al. 2010).

In an in vivo study on rats with acute pulmonary inflammation, which was induced by *Escherichia coli* LPS, photobiomodulation reduced TNF-α and IL-1β in BAL fluid. It was suggested that inhibition of TNF-α and IL-1β production might be due to ICAM-1 upregulation. There was no influence on CINC-1, MIP-2, or the expression of IL-10 after laser irradiation. GaAsAl diode laser was used in this regard. Laser parameters were as follows: 650 nm wavelength, power 2.5 mW, power density 31.2 mW/cm2, energy density 1.3 J/cm2, laser spot size 0.08 cm2, and irradiation time 42 s (de Lima et al. 2010).

da Silva achieved similar results in the reduction of lung inflammation by a diode laser (continuous mode, 30 mW, 660 nm, 60 s/point, a spot size of 0.14 cm2, a power density of 210 mW cm2, and energy density of 12.86 J/cm2). Pulmonary inflammation was induced by formaldehyde (%1). The lower number of neutrophils, degranulation of mast cells, and MPO activity were observed along with reduced levels of IL-6 and TNF-α and increased level of IL-10 in the lungs (Miranda da Silva et al. 2015).

Some studies have concluded that light could be useful for COVID-19 symptoms and also suggested that blue and ultraviolet wavelengths light could be beneficial in virus eradication. Further research is necessary to test the effectiveness of light in COVID-19 disease (Enwemeka et al. 2020).

30.8.5 Indirect Photobiomodulation

Lymphopenia is one of the main laboratory findings in COVID-19. These reduced numbers of lymphocytes may represent the lower ability of the immune system to eliminate the virus. (Lu et al. 2019)

Al Musawi et al. (2016) designed an in vitro study and found that photobiomodulation could significantly increase the lymphocyte count in whole blood samples. They used 405, 589, and 780 nm wavelength lasers with 36, 54, 72, and 90 J/cm2 energy densities for all groups. It was found that 598 nm wavelength at 72 J/cm2 fluence had the best effects. There was a significant increase in CD45 lymphocytes and natural killer (CD16 and CD56) cells. However, other cells, like CD3 T lymphocytes, T-suppressor (CD3, CD8) cells, T-helper (CD3, CD4) cells, and CD19 B lymphocytes, did not show any significant changes. As explained before, T-helper cells can influence the inflammatory cascade by releasing mediators. Therefore, photobiomodulation may be able to increase lymphocyte or natural killer cells without any exacerbation in inflammation.

Neutrophils have a critical role in ARDS pathogenesis (Oliveira Jr et al. 2014). Neutrophils undergo an influx into pulmonary tissues, and they release high quantities of cytokines, ROS, and inflammatory mediators. ROS are correlated with the severity of inflammation (de Lima et al. 2011b). Fujimaki et al. (2003) reported that photobiomodulation could attenuate ROS production in neutrophils without influencing cell viability. This effect was seen in both nonsmoker and smoker patients, but it was more pronounced in smoker patients. It was explained that MPO produces the ROS in neutrophils, and laser irradiation can reduce MPO activity. Infrared diode laser (GaAlAs) was used with parameters of 830 nm wavelength, continuous wave mode, power density 150 mW/cm2, power 1000 mW, spot size 6.6 cm^2.

30.9 Photodynamic Therapy (PDT)

The history of photodynamic therapy dates back thousands of years to the ancient civilizations of Egypt, India, and China. The ancient people discovered that administering some plants to patients and exposing them to sunlight could help the treatment of different diseases such as psoriasis, rickets, vitiligo, and skin cancer. However, about 100 years ago, Hermann von Tappeiner and Jesionek were the first to describe the photosensitization reaction and active oxygen formation, based on the accidental findings of his student

Oscar Raab, who was studying the reaction between the fluorescent dyes and microorganisms. They named the technique "photodynamic action" (Dolmans et al. 2003).

The PDT technique was successfully tested in the early twentieth century for the treatment of malignant tumors, especially skin cancer. However, due to the lack of reliable evidence, it was not welcomed by the scientific community until the 1970s. Subsequently, following Dougherty's initial studies using porphyrin derivatives, commercial photosensitizer products, and appropriate light sources were introduced, leading to successful clinical studies (Dolmans et al. 2003; Allison and Moghissi 2013).

PDT works based on the interaction between light, a photosensitizer (PS), and oxygen. ROS production due to the interaction between light radiation and nontoxic PSs can occur either inside the cell or in the immediate environment. Cellular apoptosis or cell necrosis occurs with minimal damage to adjacent tissues. Thus, an advantage of PDT is its dual selectivity, meaning that both PS and light with a specific wavelength are selectively confined to the target cells or tissue (Bargrizan et al. 2019; Saffarpour et al. 2018).

30.9.1 Mechanism of Photodynamic Therapy

Apoptosis or cellular necrosis (cellular PDT), as well as the destruction of blood vessels (vascular-PDT), results from the generation of ROS, which oxidizes biomolecules. It is the basis for the use of PDT in the treatment of various diseases, including cancers and bacterial infections.

In general, photodynamic reactions occur in two ways, one is mediated by ROS and occurs where photosensitizers are exposed to light, and the second group is related to reactions that are not caused by oxygen called photochemotherapy (Dolmans et al. 2003). After absorbing the light energy, the PS is excited to a long-lived excited triplet state. In this case, it either returns to the ground state by losing energy, or it can undergo two types of photochemical reactions called type I and type II. In the type I reaction, the transfer of energy from the PS causes free radicals in adjacent molecules, and during their reaction with oxygen, ROS (superoxide and hydroxyl radicals) are formed. In type II reactions, the PS-excited energy is transferred directly to the ground-state triplet $^3O_2$ oxygen molecule, forming singlet oxygen $^1O_2$, another type of ROS. Photodithazine and phthalocyanine are two types of PSs with the type II mechanism of action. Malachite green from the triarylmethane family is another dominant type of PS that appears to undergo the type I mechanism of action (Reis et al. 2019), as seen in Fig. 30.5.

30.9.2 PDT for Infectious Disease

An important challenge in the treatment of infectious diseases is the emergence of bacteria that are resistant to the effects of antibiotics. Therefore, many efforts have been made in recent decades to find effective treatments for resistant infections. In the case of viral infections, there are several limitations, such as the lack of effective vaccinations for viruses, different immune responses of people to vaccination, limited range of antiviral drugs, and antiviral drug resistance (Shahbaz et al. 2016). Due to the desire for targeted therapy and the failure of antibiotics, the PDT method has been proposed as an effective method in the treatment of microbial infections (Shahbaz et al. 2016; Afrasiabi et al. 2019; Ahrari et al. 2018).

30.9.3 Antimicrobial Photodynamic Therapy

Antimicrobial photodynamic therapy (aPDT), also known as photoactivated disinfection, is a new type of treatment that can inhibit bacterial, viral, fungal, and parasitic infections. aPDT is also known as photodynamic inactivation (PDI), lethal photosensitization, photoactivated disinfection (PAD), or photodynamic antimicrobial chemotherapy (PACT), and, as mentioned above, the most important application of aPDT is the

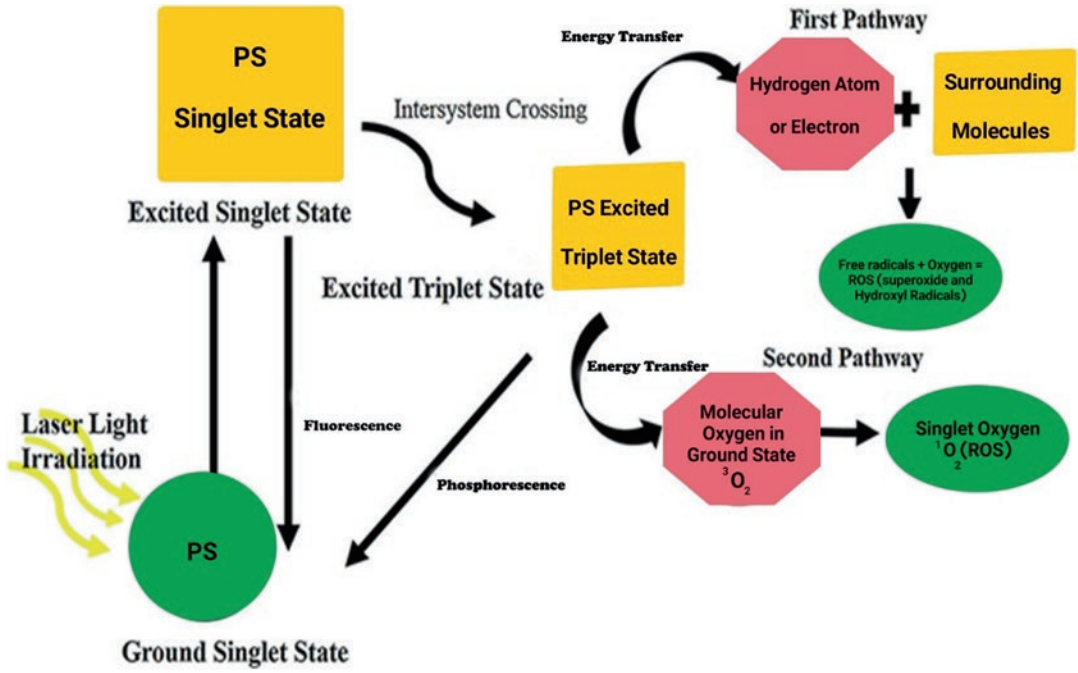


Fig. 30.5 Mechanism of photodynamic therapy

treatment of multidrug-resistant infections. The importance of aPDT treatments is such that no bacterial resistance to this method has been reported so far (Kharkwal et al. 2011).

The most important advantages of using aPDI technique include (Reis et al. 2019) lack of toxicity and gene mutations in the long run; ability to destroy microbes in a short time (a few seconds to a few minutes); no damage to adjacent tissues; the ability to access and affect areas of complex anatomy; decreased risk of bacteremia, in particular in patients with weakened immune systems; and high repeatability without antimicrobial resistance.

30.9.4 Photoinactivation of Viruses

As mentioned, aPDI can also have an antiviral function. Enveloped viruses are the most important group of viruses that are destroyed by aPDI. The presence of lipid and protein structures in the envelope plays a vital role in the possibility of PS binding to the virus envelope, and the most important mechanism for virus inactivation is protein damage (Kashef et al. 2017; Käsermann and Kempf 1998). The PDT virus inactivation mechanism is thought to be due to one or more of the following three possibilities: (i) damage to the cell membrane or virus envelope, (ii) inactivation of proteins or essential enzymes, and (iii) damage to the structure of DNA.

Cellular damage due to the effect of aPDI falls into two groups: morphological and functional. The most important functional damage is the loss of enzymatic activity, oxidation, and denaturation of proteins, as well as inhibition of metabolic processes such as DNA synthesis or glucose transport. Changes in the mesosome structure, as well as direct damage to the cell wall, are the most critical morphological damage. Damage to the cell wall causes the intracellular contents to leak and disrupt the membrane transport system (Kashef et al. 2017; Hamblin 2017).

Methylene blue (MB), or 3,7-bis(dimethylamino)phenothiazine-5-ium chloride, is an important PS that, along with light, can inactivate RNA viruses such as HIV-1 in blood or blood products. The mechanism of

action of MB in the inactivation of viruses refers to the chemical process through the stimulation of MB by light radiation and change from the ground state (MB) to an excited singlet state (^{1}MB). ^{1}MB can lose its energy and return to the ground state or become an excited triplet state (^{3}MB). ^{3}MB can also slowly lose its energy and return to the ground state or act according to type I or type II reactions. As mentioned, type II reactions take place in the presence of oxygen, and ^{3}MB is converted to the ground state by converting triplet oxygen to singlet oxygen. Singlet-state oxygen has 23 kcal more energy than ground-state triplet oxygen and has a much higher oxidizing potential. ^{3}MB can also carry out type I reactions in O2-saturated organic solvent or air-saturated aqueous solutions through H atom or electron transfer. MB can make strong bonds to DNA, especially in G-C-rich regions, and break nucleic acid strands in the presence of light (Cadet et al. 1986; Floyd et al. 2004).

30.10 Antiviral Photodynamic Therapy in COVID-19

The initial clinical applications of aPDT as a potentially effective and safe treatment modality for infectious diseases were directed against superficial viral diseases, including herpes genitalis (Chang et al. 1975; Roome et al. 1975). Besides in vitro work on different viruses, in recent years several clinical trials of systemic and topical aPDT as a treatment approach and adjuvant therapy with surgery, cryotherapy, or chemotherapy have been conducted against viral infections (Abramson et al. 1992; Bujia et al. 1993; Shikowitz et al. 1998; Zhou et al. 2014; Wiehe et al. 2019). Currently, there are two main clinical and medical aspects for aPDT of viruses: one is the treatment of local and superficial viral infections, including herpes simplex virus (HSV) and human papillomavirus (HPV) infections, and the other is the area of blood product decontamination. An inhibitory effect of aPDT was observed on human immunodeficiency virus (HIV) through the decrease of viral integrase and protease activities. Antiviral potentials of Buckminsterfullerene and its derivatives have been tested against some viruses such as HIV by several researchers. These compounds can effectively degrade HIV protease under photo-irradiation and inhibit HIV replication in living cells (Friedman et al. 1993). Many reports have also emerged over the years of the use of aPDT as a practical methodology for sterilization of blood or blood products (Lulic et al. 2009; Azarpazhooh et al. 2010). These studies generally involved long known human viruses but have also been carried out on recently emerged viruses, e.g., coronaviruses.

Several studies have revealed that lipid-enveloped viruses are more susceptible to inactivation using aPDT than non-enveloped viruses (Hamblin and Hasan 2004). Although there is no evidence explicitly investigating the effect of aPDT on viral lipids and proteins, there are investigations about the effect of ROS on viral lipids (Girotti 2001; Costa et al. 2012; Baptista et al. 2017). Since there are viral lipids in the envelope of the COVID-19, these should be sensitive to the effects of aPDT. aPDT damage to the structure of the viral envelope can inhibit the binding of the virus to the cells because the envelope plays a vital role in the attachment of viruses to the host cell surface. The effect of aPDT as an adjunct therapy for a viral infection such as MERS and influenza caused by MERS-CoV and orthomyxoviruses, respectively, can be generalized to the COVID-19 due to the similarity of viral pathogenesis to cause primarily mild to severe respiratory infections. In humans, these viruses can be detected with higher viral load and longer duration in the respiratory tract and have also been detected in feces, serum, and urine and blood samples (Ho et al. 2013; Hirose et al. 2016; Al-Abdely et al. 2019). They are highly contagious, causing millions of infections each year.

A recent study by Jin et al. (2020b) conducted aPDT with methylene blue as a photosensitizer (Table 30.1) could be effective against SARS-CoV-2 in plasma without any side effects. Previously, it has proven that methylene blue photochemical technology not only inactivates lipid-enveloped viruses in vitro but also can be applied in clinical treatment without damage to other components of the plasma (Eickmann et al.

Table 30.1 Summary of studies that used either direct or indirect methods for photobiomodulation

No	Study	Year	Induction of lung inflammation	Target tissue/ organ	Light source	Light parameters	Results
1	Aimbire et al. (2005)	2005	Airway and lung inflammation induced by gram-negative bacterial lipopolysaccharide (LPS) intravenous injection	Rat lung	Ga-Al-As diode laser	12 mW, irradiation time = 1 min 20 s, spot size = 0.08 cm2, Continuous wave	Photobiomodulation reduced RTHR, BAL and lung neutrophils influx which led to the anti-inflammatory effect. It is associated with inhibiting of COX-2-derived metabolites
2	Aimbire et al. (2006)	2006	The complex immune reaction by Instillation of Ovalbumin intrabronchial followed by IV injection	Rat lung	Ga-AsI-Al laser	650 nm, 42 s at 5 min after induction, continuous mode 0.04, 0.11, and 0.22 Joules Spot size = 0.08 cm2 Irradiated through the skin over upper bronchi	LLLT significantly reduced TNF-α expression in a dose-dependent manner. 0.11 J had the best efficacy
3	Aimbire et al. (2008)	2008	Acute lung injury induced by IV injection of lipopolysaccharide (LPS) (5 mg/kg)	Rat lung	diode laser	660 nm, 30 mW spot size= 0.785 cm2; skin over the upper bronchus	LLLT decreased lung permeability, neutrophils influx, MPO activity, IL-1β expression, and its mRNA Laser anti-inflammatory effect at 4, 12, and 24 h after LPS exposure
4	Mafra de Lima et al. (2009)	2009	TNF-a-induced acute lung inflammation	Rat-dissected bronchi with or without TNF-α	Ga-As-Al laser	650 nm, 2.5 mW, spot size = 0.08 cm2, 0.44 J, irradiation time = 42 s	Photobiomodulation reduced BSM hyperreactivity or relaxation after acetylcholine and isoproterenol application, respectively Laser irradiation decreased TNF-α mRNA expression
5	de Lima et al. (2010b)	2010	Acute pulmonary inflammation induced by aerosol of lipopolysaccharide from *Escherichia coli* (0.3 mg/ mL)	Rat lung	GaAsAl diode laser	650 nm, 2.5 mW, spot size = 0.08 cm2, irradiation time = 42 s The skin over the upper bronchus	Photobiomodulation reduced pulmonary edema, the neutrophil influx, endothelial cytoskeleton damage, TNF-α, IL-1β, and ICAM-1 expression Levels of CINC-1, MIP-2, and IL-10 did not affect by laser irradiation
6	de Lima et al. (2010b)	2010	4 h incubation with LPS or H2O2 for inducing acute lung inflammation	Rat AM cell line AMJ2-C11	diode laser	660 nm, 30 mW, spot size = 0.785 cm2, irradiation time = 252 s	LLLT decreased MIP-2 mRNA expression and intracellular ROS generation

(continued)

Table 30.1 (continued)

No	Study	Year	Induction of lung inflammation	Target tissue/ organ	Light source	Light parameters	Results
7	de Lima et al. (2011b)	2011	Acute lung inflammation induced by intestinal ischemia and reperfusion	Rat lung	diode laser	660 nm, 30 mW, 5.4 J, spot size= 0.08 cm2 Irradiation time= 3 min skin over the upper bronchus	Lung edema, neutrophils influx, MPO activity and TNF expression and production were reduced by LLL irradiation, in contrast, IL-10 production was increased
8	de Lima et al. (2011a)	2011	Acute lung inflammation induced by LPS inhalation or TNF intranasal instillation	Rat-dissected bronchi	InGaAlP laser	660 (685) nm, 8.82 J, irradiation time = 252 s On the skin over the right upper bronchus	Photobiomodulation increased The cAMP indirectly in Alveolar Macrophages by a TNF-dependent mechanism
9	de Lima et al. (2013a)	2013	Acute lung injury induced by gut ischemia and reperfusion	Rat lung	diode laser	660 nm, 30 mW, 5.4 J, continuous mode, irradiation= 180 s, spot size= 0.08 cm2 The skin over the bronchus in the direction of the trachea distal Two-series laser irradiations: (a) 5 min after initial or 5 min before the end of the intestinal reperfusion (b) 30 min after the beginning of the reperfusion	Lung edema, neutrophils influx, MPO activity, and ICAM-1 mRNA expression, ROS formation were reduced by LLL irradiation GSH concentration in the lung, HSP70, and PPARy expression were increased after LLLT Photobiomodulation reduce acute lung injury induced by gut ischemia and reperfusion
10	de Lima et al. (2013b)	2013	ARDS induced by intestinal ischemia and reperfusion	Rat lung	diode laser	660 nm, 30 mW, 5.4 J, continuous mode, irradiation= 3 min Spot size= 0.08 cm2 Skin over the upper bronchus	Photobiomodulation airway reactivity dysfunction by decreasing lung edema, MPO activity, and TNF-α, iNOS or ICAM-1 expressions LLLT increased the production of IL-10
11	de Lima et al. (2014)	2014	ARDS induced by intestinal ischemia and reperfusion	Rat lung	diode laser	660 nm, 30 mW, 5.4 J, continuous mode, irradiation = 5 min Spot size = 0.08 cm2 skin over the upper bronchus	IL-6 and TNF mRNA expression and proteins were reduced significantly the following photobiomodulation However, IL-1β and MPO activity was reduced by all doses except 1 J/cm^2 Photobiomodulation increased IL-10 protein in 1 J/cm^2
12	Oliveira Jr et al. (2014)	2014	Acute lung inflammation and ARDS induced by LPS	Rat's lung	Infra-red laser	830 nm, 35 mW, 80 s per point, 3 points per application (total 240 s), continuous mode Direct contact to skin Point 1 was in the end part of trachea, point 2 and 3 were in the right and left lungs, respectively	Photobiomodulation significantly inflammation in LPS-induced ARDS and reduced number of total cells, neutrophils in BAL or lung parenchyma and levels of IL-1beta, IL-6, KC and TNF-alpha in BAL fluid and in serum

13	Miranda da Silva et al. (2015)	2015	Lung inflammation induced by formaldehyde (1%) or vehicle inhalation (distilled water)	Rat lung	diode laser	660 nm, 30 mW, spot size = 0.14 cm^2, 60 s/point, 1.8 J for 1 min	Photobiomodulation reduced neutrophil influx (MPO activity), leukocyte number, degranulation of mast cells, and lung microvascular permeability IL-6 and TNF-α production were reduced, but IL-10 generation was increased after laser irradiation
14	de Oliveira Junior et al. (2015)	2015	ARDS induced by LPS intratracheal or intraperitoneal	Rat lung	Infra-red laser	830 nm, 35 mW, 80 s per point 3 points per application) direct contact with the skin	Photobiomodulation significantly reduced ARDS in both inducing ways Photobiomodulation decreased total cell and neutrophil count in the BAL and neutrophil count in lung parenchyma and also reduced levels of IL-1beta, IL-6, KC, and TNF-alpha in BAL and in serum IL-10 level didn't increase by photobiomodulation
15	da Silva Sergio et al. (2018)	2018	Acute lung injury induced by intraperitoneal *Escherichia coli* LPS injection	Alveolar epithelial cells of rat lung	AsGaAl diode laser	808 nm, 100 mW, spot size= 0.028 cm2, 2 and 5 J energy per point, four points of irradiation, time= 2 and 5 s per point Skin over the lung	Photobiomodulation increased Bcl-2 mRNA levels but reduced caspase-3 mRNA levels in acute lung injury Also, photobiomodulation reduced DNA fragmentation in alveolar cells but increased in polymorphonuclear cells which inducing apoptosis in these inflammatory cells
Indirect application of photobiomodulation							
16	Fujimaki et al. (2003)	2003	Isolated neutrophils from peripheral blood samples	Human neutrophils	GaAlAs laser	830 nm continuous wave, 1000 mW, spot size 6.6 cm2, irradiation time = 30 or 60 s	Photobiomodulation attenuated ROS production in neutrophils and can reduce oxidative tissue injury
17	Musawi et al. (2016)	2016	Whole blood sample		Diode laser	wavelengths of 405, 589, and 780 nm, 10 mW, spot size = 0.332 cm2, irradiation time = 20, 30, 40, and 50 min	Photobiomodulatory effects are related to laser parameter. wavelength of 589 nm and fluence of 72 J/cm2 had the best results Photobiomodulation significantly increased CD45 lymphocytes and natural killer (NK) (CD16, CD56) cells, but there was no significant change for CD3 T lymphocytes, T-suppressor (CD3, CD8) cells, T-helper (CD3, CD4) cells, and CD19 B lymphocytes

2018, 2020; Xu et al. 2005). According to the Jin et al. results, 1, 2, and 4 μM of methylene blue photochemical therapy using 630 nm wavelength light for 2 min could completely inactivate the virus, and the viral titer of SARS-CoV-2 decreased to 4.5 $\log_{10}$ median Tissue Culture Infectious Dose (TCID50)/mL.

As commented on by Eickmann et al. (2018, 2020), methylene blue plus visible light using light doses as low as 30 J/cm^2, or 25% of the standard full light dose of 120 J/cm^2, can reduce SARS-CoV and MERS-CoV by more than 3.1 and 3.3 $\log_{10}$ $TCID_{50}$/mL in plasma, respectively.

The inactivation of the MERS-CoV using a riboflavin-based and ultraviolet light-based photochemical treatment in plasma products was evaluated by (Keil et al. 2016). In this study, the treatments were performed using pooled and individual plasma units. The mean reductions in the log titer of MERS-CoV for the pooled and individual donor plasma were ≥ 4.07 and ≥ 4.42, respectively. Also, the results of this study suggested that riboflavin and UVA light might be able to reduce the risk of MERS-CoV transfusion transmission in both platelet and plasma products.

A lipophilic thiazolidine derivative named LJ001, and an arylmethylidene rhodanine derivative were described in 2010 as a new broad-spectrum antiviral compound (Wolf et al. 2010) against more than 15 different enveloped viruses. LJ001 was then introduced by (Vigant et al. 2013) as a new class of antiviral photosensitizer with increased potency, good $^1O_2$ quantum yields, and red-shifted absorption spectra. On the other hand, they determined the effects of treated influenza virus A (A/PR/8/34 H1N1) with five mM of LJ001, exposed to visible light for one h on the phospholipid composition of viral membranes. As previously reported (Lorizate and Kräusslich 2011), the lipid composition can affect the biophysical properties of viral membranes that impact the efficiency of virus-cell fusion. The results of Vigant et al. (2013) showed that LJ001-treated viruses had an up to a 300-fold increase in oxidized forms of unsaturated phospholipids. It was suggested that aPDT by LJ001 targets the viral lipid membrane and can inhibit virus-cell fusion.

In another study by Lenard et al. (1993), hypericin (4,5,7,4′,5′,7′-hexahydroxy-2,2′-dimethyl-naphthodianthrone, an anthraquinone derivative and one of the main active compounds in St. John's wort (*Hypericum perforatum* L.) (Lyles et al. 2017; Klemow et al. 2018)) and rose bengal were used as the photosensitizers during aPDT to inhibit viral fusion of the influenza virus. The finding showed that aPDT using 80 nM hypericin and a standard fluorescent lamp against the influenza virus led to an extensive cross-linking of G and M proteins and may disrupt the capacity of the viruses to attach and penetrate the host cells. Also, aPDT of the influenza virus using rose bengal at a concentration of 50 nM plus a fluorescent lamp modified the HA fusion protein and led to protein cross-links.

Chen et al. investigated the potential antiviral activity of curcumin against influenza virus propagation. The results indicated that curcumin inhibits hemagglutinin as a viral protein in influenza a virus in cell culture. Chen et al. (2010) and Sobotta et al. (2016) evaluated the photodynamic activity of copper (Cu^{2+})- and metal-free phthalocyanine, possessing 1,4,7-trioxanonyl substituents against several viruses such as parainfluenza virus-3, influenza A virus (H1N1, H3N2), and influenza B virus. In their experiments, 100 μM of this compound was exposed to the virus strains, irradiated for 30 min at 735 nm with a light intensity of 4.5 mW/cm^2 and a light dose of 8.1 J/cm^2. The average percentages of virus infectivity versus control were 4.6, <1.6, <3.3, and 30 for parainfluenza virus-3, influenza A virus (H1N1, H3N2), and influenza B virus, respectively. The findings of Sobotta et al. study indicated that photoactivation of Cu^{2+} phthalocyanine could generate various reactive oxygen species (ROS), including singlet oxygen, which leads to decrease infectivity of a wide variety of enveloped viruses. Also, one of the desired properties of phthalocyanine is that it can be activated with 735 nm wavelength in the far-red light spectrum that is not only much less damaging for nearby tissues but also in combination with phthalocyanine affords the local generation of ROS.

Phthalocyanines were used by Ke et al. (2014) due to their absorption in the tissue-penetrating red visible region, as well as production of the highly efficient singlet oxygen. In their study, the efficacy of a series of zinc (II) phthalocyanines conjugated with an oligolysine chain in photodynamic inactivation of influenza A virus (H1N1) was examined. The results showed that influenza A virus (H1N1) was susceptible to photodynamic inactivation with a half-maximal inhibitory concentration (IC_{50}) values as low as1 pM upon irradiation at $\lambda > 610$ nm under a light source of a 300 W halogen lamp with a water tank for cooling at a fluence rate of 40 mW/cm^2 for 20 min. Eventually, it was determined that phthalocyanines are promising photosensitizers for the photoinactivation of influenza A enveloped virus.

Using porphyrin-conjugated multiwalled carbon nanotubes (NT-P), the study (Banerjee et al. 2012) demonstrated the effects of visible light on inactivation of influenza A virus (H3N2). In the first series of experiments, the dependence of viral inactivation on the concentration of NT-P under 90 min light irradiation was evaluated. The virus infectivity percentage was reduced from 86% to 2% as the concentration of NT-P was increased from 0 to 1500 μg/mL. In the second series of experiments, the virus inactivation was examined using 1000 μg/mL of NT-P with different times of light irradiation from 0 to 90 min. The data showed that the percentage of virus infectivity was sharply decreased from 78% to 3% in a dose-dependent manner after increasing time of light irradiation (0–30 min). The results showed that 1000 μg/mL of NT-P and 30 min of irradiation with visible light from a compact fluorescence lamp (350 W) as the optimal dose of aPDT could cause more than a 250-fold reduction (with only 1% of virus infectivity) as the effective infectious viral dose. This inactivation was due to the production of ROS by the protoporphyrin IX (PPIX) part of NT-P in the presence of light. There was no significant reduction in the percentage of infected cells between viruses treated with NT-P in dark conditions without any NT-P under light, so this finding establishes the synergistic effect of light and NT-P. Overall, these results suggest that NT-P with light may be used effectively against influenza viruses without any emergence of resistance to treatment.

In another study, the photosensitizer and light dose dependence of aPDT for virus inactivation was also confirmed by a study from (Belousova et al. 2014). They evaluated the photodynamic inactivation of influenza virus A/Puerto Rico/8/34 (H1N1) by a solid-phase fullerene-based photosensitizer (SPFPS). In this study, an ultrabright diode at a maximum wavelength of 460 nm and a mean power density of 180 mW/cm^2 was used as the source of irradiation. Results demonstrated that the inactivation of the influenza virus depended on the concentration of SPFPS and the dose of irradiation. To confirm the obtained data, two studies were designed: first, a model containing 0.1 g/mL of SPFPS and different time periods of irradiation (10–60 min; dose108-648 J/cm^2) was used. The results showed the infectious titer of the virus was reduced with increasing irradiation dose, but it did not reach the zero level. Interestingly, some infectious virus was still detectable at the highest dose, i.e., 648 J/cm^2 (60 min) irradiation. In the next model, the highest concentration of SPFPS with the lowest dose of radiation was used. The findings showed that the virus was wholly inactivated with 2 mg/mL SPFPS at an irradiation dose of 108 J/cm^2 (30 min) irradiation. According to the data presented by Belousova et al., optimization of the aPDT conditions is important to attain complete inactivation of enveloped viruses in a relatively short time.

On the other hand, the photodynamic inactivation using hematoporphyrin of influenza A/WSN was reported by Perlin et al. (1987). It was shown that hematoporphyrin, as a pigmented, iron-free natural breakdown product of hemoglobin, has good photoactivated antiviral efficacy, which results from ROS generated by energy transfer from the light-excited pigment to oxygen. The influenza virus was inactivated entirely within 15 min of incubation with 2.5 μg/mL hematoporphyrin in the presence of a fluorescent lamp as a visible light source. In addition, it was found that guanosine monophosphate was the only nucleotide to be decomposed in the presence of hematoporphyrin and fluorescent lamp, which could

inhibit the influenza virus replication. It was revealed that no cytotoxicity could be detected with five μg/mL of hematoporphyrin against primary chick embryo fibroblasts (CEF). Inhibition of 50% of CEF cells was determined with 25 μg/mL after overnight incubation. No CEF cell destruction was seen at 50 μg/mL within 24 h. Therefore, a selective index of 100 for the antiviral effect of hematoporphyrin was calculated by the ratio of the cytotoxic concentration (50 μg/mL) to the inhibitory concentration of the virus (0.5 μg/ml).

In addition, aPDT has been tested for the treatment of recurrent respiratory papillomatosis. Goon et al. (2008), Venkatesan et al. (2012), and Hu et al. (2018, 2019), in their evaluation of the literature involving the treatment of recurrent respiratory papillomatosis, concluded that aPDT could be applied as an adjuvant treatment for viral infections.

In a randomized prospective trial, Shikowitz et al. (1998) evaluated the immediate and long-term results of aPDT using one of two doses of 3.26 mg/kg or 4.25 mg/kg dihematoporphyrin ether (DHE) for respiratory papillomatosis. The light was administered using an Aurora/M tunable Argon pumped dye laser emitting 630 nm red light through a 400 μm diameter flexible quartz fiber for 100–200 s. According to the results, there was a notable improvement and a more significant decrease in papilloma growth rate in patients receiving 4.25 mg/kg DHE. The photosensitizer DHE is highly lipophilic and binds to the cytoplasmic membrane and slowly diffuses into cytoplasm around the perinuclear area. Also, the 3-year follow-up of patients confirmed that the improvement was maintained.

Shikowitz et al. (2005), in another clinical trial study, investigated the efficacy of aPDT with 0.15 mg/kg meso-tetra(hydroxyphenyl) chlorin (m-THPC, a second-generation photosensitizer molecule based on a chlorin) for respiratory papillomatosis. Diode laser at a 652 nm wavelength as an activating light was irradiated with 80–100 J for adults and 60–80 J for children over an activation time from 200 to 330 s. The results showed there was a significant reduction in lesion severity 6–9 months after aPDT, with 45% of patients in the early treatment group free of laryngeal disease. Successful treatment of recurrent respiratory papillomatosis with aPDT has been reported, probably through an improved immune response.

A notable review by Lieder et al. (2014) provided an overview of aPDT as a relatively powerful method for local destruction of papilloma in the mucosal lining of the upper airway in recurrent respiratory papillomatosis. Although more high-quality randomized controlled trials are required to determine whether aPDT alters the course of the recurrent respiratory papillomatosis, aPDT currently continues to be used in some centers in the USA and Europe to treat recurrent respiratory papillomatosis.

aPDT, as antiviral therapy, was also investigated in a study by Kimberlin (2004), showing promise in controlled trials for juvenile-onset recurrent respiratory papillomatosis. Venkatesan et al. (2012) showed that aPDT might provide benefit by altering the immune response in the case of recurrent respiratory papillomatosis, triggering an immune response to even low concentrations of viral proteins. Moreover, other studies have shown decreased papilloma growth and potential long-term benefits (Abramson et al. 1992, 1994; Borkowski et al. 1999).

In one in vivo study, a murine model of recurrent respiratory papillomatosis was studied by Lee et al. (2010)). It was shown that papilloma completely regressed under 1.0 mg/kg phthalocyanine photosensitizer and 675 nm photoactivated light at 150 J/cm^2. As well, papilloma did not regrow within the observation period of up to 79 days.

Recently, successful treatment of adult-onset recurrent respiratory papillomatosis with CO_2 laser and aPDT was reported by Lu et al. (2019). After the patient was diagnosed with recurrent respiratory papillomatosis, CO_2 laser therapy was applied, followed by aPDT. The neoplasm was removed by CO_2 laser, and aPDT was then performed at the surgical site. During aPDT, 20% aminolaevulinic acid (ALA) as a photosensitizer was excited using irradiation of 635 nm wavelength and 120 J/cm^2 power for 30 min. Since

there was no recurrence found during follow-up 15 months after treatment, it was suggested aPDT might be an effective approach in preventing the recurrence of recurrent respiratory papillomatosis.

Altogether, recent experimental and clinical studies have revealed that aPDT is an effective approach for treating pulmonary infections. Geralde et al. (2017) evaluated the efficacy of aPDT with ICG (10 μmol/L) as a photosensitizer and extracorporeal illumination using an infrared light source with a 780 nm laser device for the treatment of pneumonia in an experimental mouse model. The findings confirmed the potential of aPDT to eliminate *Streptococcus pneumoniae* and treat lung infections by administration of the ICG and extracorporeal illumination with infrared light. Geralde et al. (2017) also assessed the effect of aPDT on alveolar macrophages as critical lung phagocytic cells responsible for innate immunity. Notably, the viability of alveolar macrophage was more than 90% following aPDT with light at 850 nm and ICG suggesting that aPDT did not harm the host immune system and could be a safe treatment modality (Geralde et al. 2017).

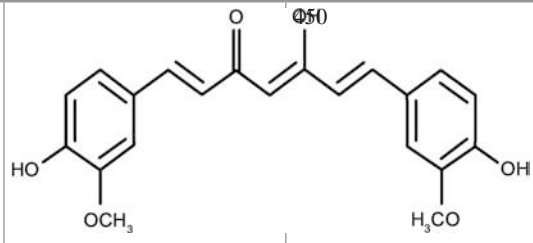
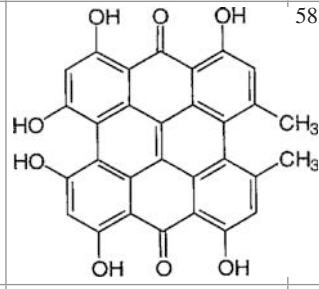
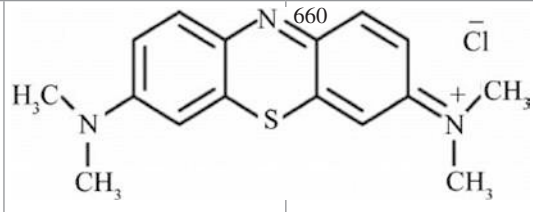
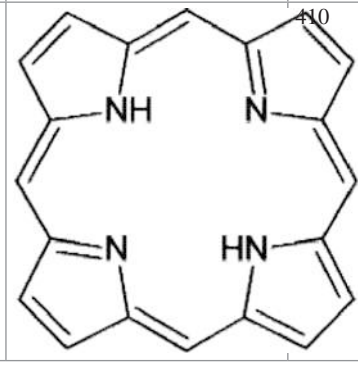
The penetration depth of the light is the main limiting factor in the widespread clinical acceptability of aPDT in the case of deeper organs and thicker lesions. Among the photosensitizers, the absorption peak of ICG is in near-infrared (810 nm) where penetration into tissues is increased due to low absorption by water, hemoglobin, and melanin, which makes ICG an ideal photosensitizer in extracorporeal aPDT applications for deep-seated lesions, which need light penetration through the lung parenchyma (Urbanska et al. 2002; Crescenzi et al. 2004).

A critical issue in the clinical use of aPDT is the efficient delivery of light. A study by Geralde et al. (2014)) revealed an insignificant reduction in the intensity of light transmittance from an 810 nm laser through the mouse chest in a post-mortem model. Based on these results, infrared light with 810 nm may be used effectively for extracorporeal application in aPDT.

Therefore, for the best use of aPDT in clinical application, it is necessary to pay attention to many factors. How the photosensitizers for aPDT are delivered into the lung environment could be via intratracheal or intravenous pathways. It has been demonstrated that these delivery routes of photosensitizers can homogeneously expose all affected areas in the lung without complications. However, the poor penetration of the activating light through to the target tissue is also a limitation in the clinical usage of aPDT (Zhang et al. 2014). According to one recent clinical trial, aPDT can be used at the oropharynx in subclinical infections in the upper respiratory tract. This method would help to reduce the microbial load and infection complications (Fekrazad et al. 2017). Some of the various photosensitizers are used in viral disease are summarized in Table 30.2.

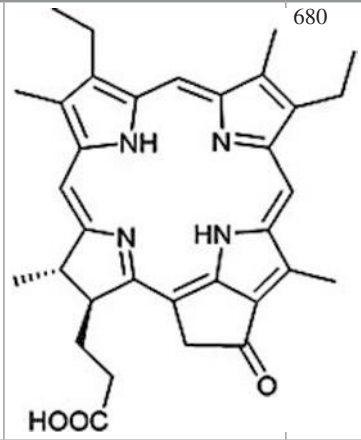
In this chapter, it was our objective to provide an overview of aPDT against viruses, including influenza viruses, MERS-CoV, and orthomyxoviruses over the last decade, to identify current applications and developments that may be useful against COVID-19. The most commonly used clinical application of the aPDT against these viruses is currently the field of viral decontamination of blood products. Looking at this field of aPDT application as an antiviral phototherapy, it becomes evident that there is no "single" specific photosensitizer, which is best suited for aPDT against viruses, but the choice of PS depends on the virus target and specific application. Given the rise of viral resistance against antiviral agents, aPDT, as a minimally invasive treatment modality, could be an alternative treatment to intractable viral diseases. It will also be important to study possible synergistic effects between aPDT and classical antiviral drugs. Although, more studies to confirm the effect of aPDT are still required, especially in photodynamic approaches to the inactivation of enveloped viruses, given this literature review of photoactivated-based treatment in the modern era, and its established safety and efficacy against the viruses that typically infected the respiratory tract, it could be

Table 30.2 Properties of some of the most widely used photosensitizers against viruses

Photosensitizers	Molecular structure	Wavelength (nm)	Target viruses
Curcumins		450	VSV FCV FHV HPV IAV HIV-1 HSV-2 HBV HCV
Hypericin		588	HSV HIV IAV VSV HCV
Methylene blue		660	HSV HIV IAV VSV HCV SV DENV ZV SARS-CoV-2
Porphyrins		410	HSV-1 HIV-1 BoHV VSV HPV

(continued)

Table 30.2 (continued)

Photosensitizers	Molecular structure	Wavelength (nm)	Target viruses
Phytochlorin		680	HPV BVDV EBV ZV HSV-1
Phthalocyanines		300–400 and 600–700	VSV HSV HIV RV IAV
Riboflavin		365–445	HIV WNV VSV IAV PPV HAV EMV SV MERS-CoV

BoHV Bovine herpesvirus, *BVDV* bovine viral diarrhea virus, *DENV* dengue virus, *EBV* Epstein-Barr virus, *EMV* encephalomyocarditis virus, *FCV Feline coronavirus*, *FHV* feline herpes viruses, *HAV* hepatitis A virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *HSV* herpes simplex virus, *IVA* influenza A virus, *MERS-CoV* Middle East respiratory syndrome coronavirus, *HPV* human papillomavirus, *NV Norovirus*, *PPV* porcine parvovirus, *RV* rhinovirus, *SARS-COV-2* severe acute respiratory syndrome coronavirus 2, *SV* sindbis virus, *VSV* vesicular stomatitis virus, *WNV* West Nile virus, *ZV* Zika virus

suggested that aPDT may be effective against COVID-19.

Many experimental and clinical studies have reported that aPDT can be applied in combination with other therapeutic modalities, including supportive therapies, chemotherapy, and surgery. aPDT could be a new adjuvant therapy to the management of viral lung diseases and reduce the proximal extent of the infected tissue. Therefore, the main indications for the use of aPDT in the clinical management of viral lung disease are the early stage of the disease, superficial, local, peripherally and centrally located affected endobronchial tissue, and pleural disease.

30.11 Conclusion

We have discussed the possibility of using PBM and photodynamic therapy for COVID-19. The best approach may be a combination of both methods, as mentioned earlier. PDT would be useful for virus destruction, while PBM would be better for improving tissue oxygenation and reduction or inhibition of the cytokine storm that occurs in severe inflammation. When PDT and PBM combined, we can reach these goals with minimal interference with medications and battle this disease with biophysical methods. The use of aPDT could be improved by using monoclonal antibodies to target lung tissue spe-

cifically. PDT can be improved by using nanotechnology to prepare more effective photosensitizers in the nanoscale and more improved targeting of lung tissue to obtain better results. Further animal and human studies are required before we can reach an optimal protocol. This chapter could encourage other scientists to work on this new pandemic problem.

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