

# Photodynamic Therapy as a New Technology for Inactivation of Coronavirus Disease (COVID-19)

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## Abstract

**Purpose:** Coronavirus Disease (COVID-19) could be an emerging disease with a severe acute respiratory infection, and its epidemiology and unique medicinal properties are perpetually increasing. Regarding the lack of COVID-19 controls, this needs current technical events to worsen and treat. Antiviral Photodynamic Therapy (aPDT) could also be effective in reducing and inhibiting the coronavirus. aPDT with various photosensitizers is a very favorable procedure to manage viral infections.

**Materials and Methods:** A total of 37 articles related to the publication of this review manuscript were mentioned. Several scientific databases such as Scopus, PubMed, Web of Science (ISI), and Google Scholar have checked the key phrases of COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), photodynamic therapy, and antiviral photodynamic therapy. All 50 main studies were found, and 37 related studies were deemed suitable for this study after review.

**Results:** Studies have shown that aPDT with different photosensitizers can be used to treat viral lung complications caused by infectious pathogens such as Middle East Respiratory Syndrome (MERS), SARS-CoV-2, and influenza. Recent studies have shown that aPDT-mediated Methylene Blue (MB) can help control and eradicate coronavirus. In general, more research is needed to use antiviral photodynamic therapy to control COVID-19.

**Conclusion:** Regarding the lack of treatment for COVID-19, MB-mediated aPDT can help reduce the impact of COVID-19. More evidence is needed to support aPDT as a treatment (SARS-CoV-2).

**Keywords:** Photodynamic Therapy; Respiratory Tract Infections Disease; Photosensitizers; Viral Infections; Coronavirus Disease.

## 1. Introduction

On December 31, 2019, a group of patients with symptoms of pneumonia was reported from an unknown source in Wuhan, Hubei, China. Shortly afterward, Chinese health officials confirmed that this group was related to a new Coronavirus 1 and was named Coronavirus disease (COVID-19) by the World Health Organization (WHO) in February 2020. Because of a single-stranded Ribonucleic Acid (RNA) virus, COVID-19 is popularly called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Since the COVID-19 outbreak began, COVID-19 has affected more than 109, 506, 025 patients in 221 countries and has become one of the largest global health crises [1, 2]. The expansion of the COVID-19 pandemic has been considered particularly due to the lack of vaccines and antiviral drugs to prevent and treat viral infections [3]. The intensity and necessity of COVID-19 desperately need the event of novel approaches for the prevention and treatment of the infection sickness. One among these strategies is often Antiviral Photodynamic Therapy (aPDT) [4]. aPDT is probably important as a possible treatment for the inhibition and decrease of coronavirus. In various studies, the efficacy of aPDT within the inactivation of the mammalian virus was confirmed. A wide variety of those are such as the Human Immunodeficiency Virus (HIV); Herpes virus; Hepatitis viruses A, B and C, parvovirus B19; human cytomegalovirus (HCMV); and adenovirus. Study results have shown that enveloped viruses are more sensitive to aPDT than non-enveloped viruses (Table 1) [5-14]. Currently, aPDT is widely used to inactivate viruses in various biological fluids such as blood. aPDT is also very effective in treating superficial viral lesions [15, 16]. The aPDT comprises three key components: a photosensitizer [17], an appropriate wavelength of light, reactive oxygen species (ROS) [18-20]. The mechanisms of aPDT have resulted in several ways in which clinical benefits are achieved. And then it gets exciting, it ends up in the ROS assembly. Light can influence intracellular activity such as cell metabolism, increased Adenosine Triphosphate (ATP) and blood flow rates, ROS modulation, angiogenesis stimulation, impaired collagen synthesis and decreased transcription factors. A wide variety of microbes, including gram-positive and gram-negative bacteria, fungi, viruses, and protozoa, have confirmed susceptibility to aPDT [18, 21-13]. This work aimed to

investigate various possible therapeutic effects of aPDT in the treatment of COVID-19.

## 2. Materials and Methods

A total of 37 mentioned papers related to the issue of this review manuscript. Various scientific databases as Scopus, PubMed, Web of Knowledge (ISI), and Google Scholar had been through COVID-19, SARS-CoV-2, Photodynamic therapy, Antiviral Photodynamic therapy key phrases. All 50 primary studies were found and after review, 37 relevant studies were considered suitable for this study.

### 2.1. Principle of Photodynamic Therapy (PDT)

The aPDT was useful to directly inactivate microorganisms (bacteria, viruses, and fungi) by photosensitizers mediated. aPDT also indirectly weakens the organism by stimulating the immune system [24]. Since the first decades of the last century the virus inactivation has been done by PSs. PDT has been used clinically against viruses for the first time since the 1970s [25]. A suggestion about the potential efficiency of aPDT against SARS-CoV-2 was formulated relatively recently, and brief results on the usage PDT in humans have also been published [26, 27]. The main target of the action of aPDT is the structures of the virus such as the capsid, the envelope and the RNA or Deoxyribonucleic Acid (DNA) of the virus [28]. With regards to the arrangement of the coronavirus and the effectiveness of aPDT against other viruses, this technique can be suggested as a complementary treatment. aPDT can affect the coronavirus as explained below. aPDT comprises the use of visible light, which is implemented with a photosensitizer (PS) [2] and with O<sub>2</sub> (Figure 1). The reaction between the light and the PS leads to the



**Figure 1.** The mechanism of antimicrobial photodynamic therapy

ROS: reactive oxygen species, PS: photosensitizer

**Table 1.** The potential targets of aPDT against SARS-CoV-2 and other viruses

First Authors	Viruses	PDT Components		Virus Target	Reference
		Photosensitizer	Wavelength		
Svyatchenko	SARS-CoV-2	Methylene blue and Radachlorin	662 nm 16 J/cm <sup>2</sup> -40 J/cm <sup>2</sup>	Spike protein-ACE2 receptor	[5]
Marcia Christina	SARS-CoV-2	Methylene blue	660 nm-808 nm 32.14 J/cm <sup>2</sup>	Envelope	[6]
Lucas D. Dias	SARS-CoV-2	Indocyanine green	780 nm 120 J/cm <sup>2</sup>	Replication	[7]
Changzhong Jin	SARS-CoV-2	Methylene blue	630 nm	DNA- ACE2 receptor	[9]
Mathieu Gendrot	SARS-CoV-2	Methylene blue	-	DNA	[10]
Rywkin	HIV	AlPcS40H	780 nm 25-28 mW/cm <sup>2</sup>	DNA	[11]
Fabian Kasermann	Semliki Forest virus (SFV), vesicular stomatitis virus (VSV)	C <sub>60</sub>	535 nm	Protein structure	[12]
L. Nikolaeva Glomb	Bovine viral diarrhea virus (BVDV), Influenza virus A(H3N2), Poliovirus type 1 (PV-1), Human adenovirus type 5 (HAdV5)	GaPc1 (Ga4), GaPc2 (Ga8), InPc1 (In4), HpD	535 nm 100 mW/cm <sup>2</sup> -50 J/cm <sup>2</sup>	Envelope	[13]
Bachmann	HIV	Methylene blue	105-110 W/m <sup>2</sup>	RNA	[14]

making of free radical species and H<sub>2</sub>O<sub>2</sub> [19]. Free radicals are created in reaction by aPDT. The subsequent destruction to DNA is moreover called oxidative damage to DNA. Free radicals damage the RNA of the virus, which means an end to the multiplying and also the infection possible of the virus. Hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) has been utilized as a disinfectant for several years.

## 2.2. Clinical Application of PDT for SARS-CoV-2 and Virus Infection Treatment

A recent review reported that using 0.5% H<sub>2</sub>O<sub>2</sub> for one minute as a surface disinfectant may be beneficial because of its anti-coronavirus antiviral activity [29]. A study published by R Mentel assessed the efficacy of H<sub>2</sub>O<sub>2</sub> on diverse viruses such as (Adenovirus types 3 (Ad3) and Adenovirus types 6 (Ad 6), Adeno-Associated Virus (AAV), rhinoviruses 1A, 1B, and type 7, myxoviruses, influenza A and B, human Respiratory Syncytial Virus (hRSV), strain long, and coronavirus strain 229E. Their results showed that corona and influenza viruses were viewed to be the most susceptible [30, 31]. Previous studies have used H<sub>2</sub>O<sub>2</sub> as a disinfectant against norovirus [32]. It is suggested that H<sub>2</sub>O<sub>2</sub> derivatives like hydroxyl

radicals are responsible for cell damage inside the cell. A diversity of enzymes have been shown to be deactivated by H<sub>2</sub>O<sub>2</sub>. Membrane destruction from ROS is observed as an accumulation of lipid peroxides, the loss of the diffusion barrier to membrane impervious indicators, and cell lysis [33, 34]. The ROS is produced during the photoinactivation procedure performance upon different serious biomolecule goals, for example, proteins, lipids, and DNA [35, 36]. The oxidative stress induced by ROS causes irreversible damage to the proteins and lipids of the virus structure [17, 37]. ROS induces apoptosis and necrosis without damaging adjacent tissues. With aPDT, both intracellular and extracellular ROS are released [38].

PS is an important part of aPDT [39]. The rapid absorption of PS by the object outside the microbial structures compared to the PS absorbed by the host (a few minutes versus several hours) and the use of locally directed light, the optional preparative therapeutic benefit of this method compared to simple antimicrobial agents such as e.g. antivirals and antibiotics [23, 40]. The ideal PS for the aPDT of porphyrin, chlorine, and phthalocyanine derivatives are the colors of porphycenes and phenothiazines, for example, Toluidine Blue O (TBO), methylene blue,

and azure are useful [18, 41]. Chloroquine ( $C_{18}H_{26}ClN_3$ ) is currently used to treat COVID-19. It is structurally correlated with MB ( $C_{16}H_{18}ClN_3S$ ) [42-44]. Primary information from a recent study suggests that MB could be an appropriate treatment for flu-like illnesses, such as COVID-19 [42-44]. In addition, some direct antiviral effects have been reported for MB [18, 41]. In addition, there is also evidence in the study that MB may have antiviral in vitro activity, even if there is no light activation, as MB showed virucidal activity when incubated with SARS-CoV-2 [44]. In addition, it has been shown that MB inhibits the SARS-CoV-2 spike protein and its Angiotensin-Converting Enzyme 2 (ACE2) receptor, which is crucial for the inactivation of the coronavirus [45]. The DNA is irradiated with light and prevents the transmission of pathogens. PDT with photosensitizers, for example, MB, which can inactivate various viruses such as Zika, yellow fever, dengue fever, Ebola viruses, and the coronavirus of respiratory syndrome in the Middle East Respiratory Syndrome (MERS-CoV) in plasma [46-50]. In addition, MB inactivated hepatitis C virus in MB-perfused transplant organs [51]. MB-mediated PDT also has antibacterial activity. It is useful in COVID-19 patients with a secondary infection. In contrast to antibiotics, after repeated exposure to aPDT, which may be suitable for the treatment of secondary infections in COVID-19 patients, there is little or no risk of developing resistance [17, 10]. While the coronavirus mainly affects the lower respiratory tract, such as the lungs, it is quite easy to endoscopically irradiate these internal structures through an optical fiber that can be presented through the nose, suggesting that aPDT is inactivating the virus and can convey in the lungs. aPDT has been recognized for the treatment of lung cancer for years and with good results [53], so aPDT can inhibit the entry of respiratory viruses, for example, SARS-CoV-2, another coronavirus, as well as respiratory viruses. Through the upper respiratory tract, when the nostrils are exposed after the addition of a PS. In fact, there have been some uses to date to inactivate microorganisms in the nasal passages by PDT [53].

### 3. Conclusion

This study aimed to evaluate the aPDT and its effects on HIV, influenza viruses, MERS-CoV, and orthomyxoviruses, which have been established over the last decade, in order to present their areas of application and advances as well as their possible therapeutic influence

on COVID-19; a valuable, beneficial, non-invasive, and irresistible method of treatment for treating diseases caused by infectious agents. Recent research shows that aPDT will be adequate in treating COVID-19 with fewer side effects and drug interactions. This system was undeniably economical as a completely unique add-on treatment for treating diseases of the respiratory organs caused by infectious agents. This study will encourage various researchers to work on this new platform. This could be valuable support against diseases caused by infectious agents due to increased resistance to antivirals, while recent studies have confirmed this hypothesis. In general, any study on the use of aPDT for the management of COVID-19 is required.

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