Photodynamic Therapy: A Rational Approach Toward COVID-19 Management

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Received: November 13, 2020 | Revised: February 08, 2021 | Accepted: February 24, 2021 | Published: March 11, 2021

Abstract

Photodynamic therapy (PDT) for the inactivation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) might be a valuable therapy for the treatment of coronavirus disease 2019 (COVID-19) disease. The spread of the SARS-CoV-2 virus has caused the COVID-19 pandemic, resulting in the death of many people worldwide due to the lack of effective treatments. FDA has recently approved two mRNA-based vaccines for emergency use, but still vaccine supply is limited. Therefore, it is imperative to discover new therapeutic strategies for the management of COVID-19 patients. PDT has been used to deactivate microorganisms for many years and might be an effective and promising therapy for COVID-19 patients. The PDT procedure is composed of a photosensitizer, light, and oxygen, which generate a local spurt of reactive oxygen species that can inactivate enveloped viruses and microorganisms. PDT is a safe, faster, cost-effective, and simple method to inactivate microorganisms. In addition, there have been no reports of resistance, unlike other antibiotics and antiviral drugs. This review aims to update the advancement of PDT and the findings could attract clinical attention in future clinical trials.

Introduction

The on-going coronavirus disease 2019 (COVID-19) pandemic is a threat to human health. Cases of COVID-19 were first reported in December 2019, Wuhan, China. Then, gene sequencing identified that COVID-19 was caused by an enveloped RNA Beta-coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The COVID-19 was declared a pandemic on 11 March 2020 by the World Health Organization. The SARS-CoV-2 virus has phylogenetic similarity to SARS-CoV that caused an outbreak in February 2003 and any terminal cancers. In the US, people aged >65 years account for 31% of cases and people aged >85 years for 6% of cases. This is alarming because these patients account for 53% of intensive care unit administration and 80% of deaths. Case-fatality rate increases with age. Therefore, it is important to discover new therapies to save patients from COVID-19 related death.

Approved therapeutic strategies for COVID-19 and limitations

SARS-CoV-2 infection currently depends on the detection of viral RNA by RT-PCR and virus-specific antibodies. Therapeutic
strategies for COVID-19 include the inhibition of SARS-CoV-2 replication and inflammation to limit tissue damages.\textsuperscript{12,13} The drugs include antiviral drugs, Veklury (remdesivir), Favipiravir, Arbidol, Janus Kinase (JAK) inhibitor, Baricitinib (Olumiant), and convalescent plasma for hospitalized COVID-19 patients.\textsuperscript{13,14} Second, monoclonal antibodies, such as bamlanivimab, casirivimab, and imdevimab have been approved for emergency use for severe COVID-19 patients.\textsuperscript{35} Other treatments, such as autophagy inhibitor chloroquine, anti-inflammatory dexamethasone, and methylprednisolone, have been used in clinics.\textsuperscript{16}

Recently, out of 52 potential vaccine candidates two vaccines, BNT162b2 from Pfizer/BioNTech and mRNA-1273 from Moderna has received Emergency Use Authorization from FDA and other vaccines are in clinical Phase 3 trials.\textsuperscript{17,18} Two COVID-19 mRNA vaccines, BNT162b2 and mRNA-1273, have been approved for use in patients aged \( \geq 18 \) years.\textsuperscript{19,20} The main side effects of the vaccines are fatigue, fever, muscle or joint pain, and headache, which are mild and self-limited. Infrequently, some vaccine recipients might develop seizures and anaphylaxis and need to be carefully monitored immediately after vaccination. Due to the limited number of vaccines and the difficult conditions required for transportation, it will take a long time to vaccinate most of the population in western countries and it might be difficult to supply it to many developing countries. This, combined with new SARS-CoV-2 mutant variants that have recently appeared, means that it is difficult to used vaccines to control the COVID-19 pandemic worldwide in a short time.\textsuperscript{17,19,21}

Hydroxychloroquine and chloroquine are antimalarial drugs that have been used for the treatment of chronic discoid lupus erythematosus, rheumatoid arthritis, and systemic lupus erythematosus in adults. Because of their anti-autophagy activity, they have been used in the treatment of COVID-19 patients. However, the therapeutic efficacy remains under debate and the US FDA caution against their use for the treatment of COVID-19 patients due to their potential cardiac side effects, including QT prolongation, ventricular arrhythmias, and cardiac toxicity.\textsuperscript{22–24} In addition, corticosteroid types of drugs for COVID-19 might increase lung injury.\textsuperscript{25,26} Therefore, it is crucial to identify an alternate approach to COVID-19 treatment, in particular, for seriously ill patients. Because the development of a new drug usually takes many years,\textsuperscript{27} repurposing the existing therapeutics that are effective against viruses that are similar to SARS-CoV-2, could be valuable to save lives.

**Principle of photodynamic therapy (PDT)**

PDT has been known for over a century and has been used for the treatment of various cancers, diseases, and infections. PDT employs photosensitizer dyes to absorb visible light to primarily form the excited singlet state, which eventually transforms into the excited triplet state. This is subjected to photochemical reactions with oxygen to produce reactive oxygen species (ROS) that are toxic to pathogenic microorganisms, cancer cells, and injured tissue.\textsuperscript{28} PDT is a unique technique to kill various pathogens, including bacteria, fungi, viruses, and parasites.\textsuperscript{29} Therefore, PDT is called photodynamic antimicrobial chemotherapy (PACT) and photodynamic inactivation (PDI).\textsuperscript{30,31} PDT was recognized as a therapy a century ago when it was observed to kill *Paramecia* and this was attributed to the combined action of drugs, for instance, acridine orange (a photosensitizer dye) and sunlight.\textsuperscript{32} Then, in 1930 this therapy was shown to display antiviral activity.\textsuperscript{33,34}

The principle of PDT involves the activation of a photosensitizer, which responds to light and leads to the production of ROS that kills microbes.\textsuperscript{35,36} Therefore, to kill microbes PDT depends on the photosensitizer (PS), photons, and ROS. Every PS absorbs a specific wavelength of light. On activation, PS is in the specific excited state, which is short-lived and lasts for nanoseconds. After electron transfer from one state to another, this short-lived state converts into the triplet state, which lasts microseconds, for instance, long-lived. Then, it enters Types 1 and 2 photochemical pathways to promote ROS production. In the Type 1 pathway, electron transfer occurs from the triplet state of PS, which leads to the formation of hydroxyl groups (HO) and the Type 2 pathway follows the energy transfer that produces singlet oxygen radicals (\( \text{O}_2^\cdot \)). The resulting ROS is highly reactive and causes oxidative stress, which leads to serious damage to biomolecules, such as nucleic acids, proteins, and lipids as well as microbes.\textsuperscript{36,37}

**Factors regulating PDT action**

Several factors regulate the efficacy of PDT, such as the concentration, nature, shape, number of PS, number and nature of radicals, and the intensity, nature, type, and wavelength of photons.\textsuperscript{35,38–41} The PSs are nontoxic and they become toxic to target tissues after illumination by light at a specific wavelength. Currently, different types of endogenous and exogenous PSs have been developed and used for interventions in different diseases.\textsuperscript{42} Therefore, the characteristics of PS and light are important in PDT to treat a variety of diseases, which depends on the causative agents.\textsuperscript{43}

The best PS must absorb light efficiently at a fixed wavelength between 630 and 700 nm. The PS must have appropriate energy in the triplet state; therefore, it can provide sufficient energy to produce ROS when transferring to its ground state. In addition, the PS should have a high quantum yield of ROS due to its high photosensitivity.\textsuperscript{44} The PS must exhibit non-toxic properties in the absence of light. The ideal property of PS is that it should have a cationic charge, which is more effective than negatively charged biomolecules.\textsuperscript{45,46} In addition, PS can be delivered intravenously, topically, or by another route into the body, such as via light sources through an endoscope, needle, and fiber.\textsuperscript{47,48} Chlorophyll derivatives, curcumin, vitamin B2, methylene blue (MB), and porphyrins have been used as PS.\textsuperscript{49–51}

The therapeutic effect of PDT on solid tumors in a deep organ depends on the intensity of excitation light. NIR light and X-rays have profound permeation depth into the tissues and NIR lasers directly excite several PSs.\textsuperscript{52} In contrast, UV-VIS excite most clinically approved PSs.\textsuperscript{53} Laser lights, halogen lamps, LEDs, and plasma discharge lamps that have different wavelengths of ultraviolet, blue, and violet lights have been used in PDT.\textsuperscript{51,54,55} Laser lights that have multiple wavelengths have specific targeted actions and laser lights with a blue wavelength are more effective for viral inactivation and reduction. However, laser lights with a green or red wavelength are best for oxygenation and ATP production, respectively. To achieve instant microbial inactivation, light sources with violet and ultraviolet wavelengths usually have strong antimicrobial activity.\textsuperscript{51} Lasers, such as argon, quartz halogen, and xenon, are efficient at 488–514 nm, 620–640 nm, and 600–700 nm, respectively.\textsuperscript{56} In antimicrobial activity, UVA lamp UV801 KL at 315–400 nm, LEDs at 470 and 625 nm, and white light lamp at 380–770 nm are the most efficient against *Clostridioides difficile*, *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aerugi nosa*, respectively.\textsuperscript{57–60}

**DOI:** 10.14218/JERP.2020.00036  |  Volume 00 Issue 00, Month Year
COVID-19, researchers are developing new therapies to fight it. Some treatments and medicines have shown promising outcomes in clinical trials and have been approved for clinical applications to combat SARS-CoV-2. Of interest, a recent study suggested PDT as an alternative therapy for SARS-CoV-2 infection in 2020. However, no clinical study has been reported.

The SARS-CoV-2 virus is a new enveloped beta-coronavirus and 82% of its genomic sequence is similar to SARS-CoV. A previous study demonstrated that PDT inactivates SARS-CoV. The SARS-CoV-2 virus consists of four structural proteins: (1) envelope (E); (2) membrane (M); (3) nucleocapsid (N); and (4) spike (S). Theoretically, the enveloped proteins of the SARS-CoV-2 virus could be deposited by PS because PDT induces ROS, which destroys many biomolecules with an optimal PS and light, in particular, for the enveloped SARS-CoV-2 virus.

PDT for antimicrobial pathogen treatment

PDT has been used to inactivate viruses as a substitute treatment for diseases that are induced by virus infection and as a strategy for environmental viral decontamination. The mechanisms that underlie the action of PDT are the irradiation of a dye with light and the successive production of ROS that destroy the virus by targeting viral nucleic acids, lipids, and proteins. In clinics, PDT has been used for the refinement of blood and the treatment of human papillomavirus (HPV) infection. In public health, PDT has been used for water and surface decontamination and biosafety. Herpesvirus infection can induce different types of diseases, which depend on the type and where herpesvirus infection occurs. Previous studies have shown that the PDT is effective for some Herpes simplex virus (HSV1 and 2) infection-induced mucous membrane and skin diseases, such as Herpes labialis (oral), keratitis (ocular), as well as Herpes zoster infection. In addition, PDT is effective for HPV infection-induced laryngeal papillomata using dihematoporphyrin ether and hematoporphyrin derivative. However, whether PDT could benefit patients with HPV-induced early stages of cervical cancer needs to be investigated.

Because pathogenic organisms develop resistance to antibiotics, alternative strategies have been implemented to control infectious diseases. PDT is promising to control infectious diseases that are caused by bacteria, yeasts, and protozoa. Furthermore, PDT stimulates the immune response to enhance the defense against infectious pathogens. PDT has been used to treat eye disorders and dermatological diseases in India, Egypt, and China for many years. Recently, PDT has been used in several localized microbial infections, in particular, for multidrug-resistant microbes due to its rapid efficacy. More importantly, PDT is effective in fighting biofilms, such as dental biofilms, chronic wound infections, oral candidiasis, ventilator-associated pneumonia, and chronic rhinosinusitis. Microbial biofilms are involved in approximately 80% of all bacterial and fungal infections in humans. Pathogens that involve biofilm formation are usually resistant to commonly used antibiotics. The biofilms contain many bacteria and fungi and occur in different functional organs of the body and are associated with middle ear infection, gingivitis, urinary tract infection, periodontitis, catheter infection, and others. In addition, PDT can eliminate wound infections that are induced by S. aureus, coagulase-negative staphylococci, Enterococcus faecalis, P. aeruginosa, Enterobacter cloacae, Peptococcus magnus, and anaerobic bacteria.

The mechanisms that underlie antimicrobial pathogens depend on the different actions of PS and light. MB can penetrate viral membranes and damages the DNA of viruses, such as HSV1 and bacteriophage M13 with distinct concentrations in response to varying intensities of light. MB is involved in RNA and enveloped protein damage in various viruses, such as human immunodeficiency virus (HIV) and vesicular stomatitis virus. Many radicals have different results, Type 1 radicals target sugar moieties, for instance, singlet oxygen is sensitive to the guanine nucleotide. MB and riboflavin inactivate coronaviruses and might target SARS-CoV. The authentic and osmium-based compounds are activated by light in the range of 400–675 nm and selectively destroy different types of tumor cells. The action of different PS components with respective viral molecular targets is given in Table 1.

Potential use of PDT against COVID-19

Research data has supported the theory that PDT is one of the safest procedures to combat viral infections. Due to the spread of COVID-19, some treatments and medicines have shown promising outcomes in clinical trials and have been approved for clinical applications to combat SARS-CoV-2. Of interest, a recent study suggested PDT as an alternative therapy for SARS-CoV-2 infection in 2020. However, no clinical study has been reported.

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It is noted that the molecular structure and charge of microbial pathogens are crucial for the efficacy of PDT because PS usually has a positive charge. ROS targets the guanine nucleotide to inhibit viral replication. The activated PS could easily target cysteine, L-histidine, tyrosine, methionine, and tryptophan to change their associated protein structure and functions. The hydroxyl group and singlet oxygen radical react differently to their targets. The singlet oxygen reacts more efficiently on viruses than other radicals and effectively targets guanine residues and tyrosine; histidine and tryptophan. It was speculated that PDT, through ROS and singlet oxygen, might target guanine residue and cysteine, L-histidine, tyrosine, methionine, and tryptophan to destroy the SARS-CoV-2 virus and limit the spread of COVID-19.

Previous studies demonstrated that PS, such as MB and riboflavin inactive coronaviruses. Schikora et al. speculated that some PS might be effective at destroying SARS-CoV-2 virus, similar to photobiomodulation (PBM) therapy, by combining different wavelengths of lights including blue, ultraviolet, and violet with several PS, such as curcumin, chlorophyll derivatives, vitamin B2, and MB. An intravenous approach with blue light might be efficient using green-based PS, such as indocyanine. It was speculated that a combination of PDT and PBM might achieve better results for the treatment of COVID-19 (Fig. 1).

Cytokine storm and treatment options

Aberrant cytokine responses or cytokine storm are associated with disease progression and death in COVID-19 patients. It is well known that viral infections enter the cells through a specific receptor on the targeted cell membrane surface. It then releases components, such as RNA and DNA as pathogen-associated molecular patterns, which are recognized by pattern recognition receptors on innate immune cells, which stimulates inflammatory cytokine and chemokine production. Therefore, the control of the cytokine storm is critical to reducing the death rate of COVID-19 patients. Corticosteroid, intravenous immunoglobulin, and Ulinastatin have been used for the treatment of severe COVID-19 patients, because of their strong anti-inflammatory activity. Because the high levels of ROS might destroy innate immune cells, PDT, or a combination of PDT and PBM might be effective to control the aberrant inflammatory responses.

Sonodynamic Therapy: Analogous therapeutic approach

Sonodynamic therapy (SDT), a specific type of PDT, uses ultrasound as a light to activate PS. Of note, ultrasound penetrates the...
| Viruses                  | Viral targets                  | PDT components      | Mechanism of action/damage                                      | References |
|-------------------------|-------------------------------|---------------------|-----------------------------------------------------------------|------------|
| Mammalian+Bacteriophages| Viral membrane                | MB PS               | Penetration                                                    | 79         |
| Mammalian+Bacteriophages| Guanine residues              | Singlet Oxygen (Type 2) | Oxidation leads to destruction                                 | 81         |
| Mammalian+Bacteriophages| Sugar Moieties                | Radicals (Type 1)   | Attack on sugar moieties leads to DNA destruction               | 81         |
| T4 phage                | Nucleic acids                 | Cationic Porphyrins PS | Bind through intercalation into base pairs and destroy DNA     | 50,86      |
| HSV-1                   | DNA damage                    | MB PS + Light       | Degradation                                                    | 78         |
| HSV-1                   | DNA replication               | MB PS + Light       | Inhibited                                                      | 78         |
| M13                     | DNA                           | MB PS + AlPcS4 PS   | Strand breaks and addition of piperidine bonds lead to damage  | 77         |
| VSV                     | RNA damage                    | Phthalocyanine derivatives | Degradation                                            | 77         |
| VSV                     | RNA polymerase                | Chlorophyll derivatives + red light illumination | Decrease RNA polymerase activity | 61         |
| VSV                     | RNA complex                   | AlPcS4 PS + MB PS   | RNA degradation might result                                   | 86         |
| VSV                     | Viral envelope                | MB PS + phthalocyanine PS | Inhibit degradation of viral envelop with Vero cells   | 77         |
| HIV-1                   | RNA                           | MB PS + Light       | Destruction of RNA                                             | 80         |
| Bacteriophages          | RNA damage                    | MB PS+ rose bengal PS | Degradation                                                   | 87         |
| HSV-1                   | Viral envelope                | Meroceanine 540 PS  | Loose the ability to attach to host cell                       | 88         |
| HSV                     | Protein                       | Phthalocyanine PS   | Induce cross links                                             | 88         |
| HIV                     | Enveloped protein             | Porphyrins PS       | Inhibit cell fusion activity                                   | 89         |
| Vaccinia virus          | Histidine                     | Rose bengal PS      | Oxidation                                                      | 90         |
| Influenza and Sindbis virus | Enveloped proteins          | Hypericin PS        | Loose the ability to attach to host cell                       | 91         |
| Coronaviruses            | Nucleic Acid                  | MB PS and riboflavin PS | Damage to nucleic acid results in no replication       | 84,85      |
| Multiple viruses        | Tyrosine, histidine, and tryptophan | Singlet Oxygen   | Oxidation                                                      | 83         |
| Retrovirus              | Reverse transcription         | Chlorophyll derivatives+ red light | Inhibition                                                | 92         |

MB, Methylene blue; PS, Photosensitizer; HSV-1, Herpes simplex virus 1; AlPcS4, Aluminum phthalocyanine tetrasulfonate; VSV, Vesicular stomatitis virus; HIV-1, Human Immunodeficiency virus 1.
In addition, ultrasound causes the poration phenomenon of the cell membrane, termed sonoporation. Previous studies have shown that SDT combined with PS, such as porphyrin xanthene, TiO$_2$, and fluoroquinolone antibiotics, effectively inactivate bacteria. Other data indicates that SDT eradicates bacteria, viruses, parasites, and other microbial entities. However, there are no reports available on whether SDT inactivates the SARS-CoV-2 virus.

**Clinical application of PDT for SARS-CoV-2 treatment**

During the pathogenic process of COVID-19, the SARS-CoV-2 virus infects nasal and oropharyngeal membrane epithelial cells through its receptor, angiotensin-converting enzyme 2, which spreads into alveolar epithelial cells, in particular, type II alveolar epithelial cells. SARS-CoV-2 virus infection damages these cells and causes inflammation and pneumonia, and their disease progression leads to a cytokine storm and multiple organ dysfunction syndromes, as well as death. Therefore, the control of SARS-CoV-2 virus replication is crucial to limit the progress of COVID-19. PDT might be effective because it inactivates viruses and reduces viral load in nasal and oropharyngeal membrane epithelial cells. PDT can be carried out by the nebulization of PS into the respiratory tract or by using a catheter to deliver light. Many groups are establishing a PDT protocol for the treatment of COVID-19 as PDT inactivates other virus-related respiratory diseases, and an RNA virus is also more sensitive to PDT inactivation. Recently, a study reported the successful use of PDT in the disinfection of oral and nasal cavities in patients with early-stage COVID-19. Further studies are required to validate the findings and test the therapeutic efficacy in patients at different stages of COVID-19.

**Future directions**

Although PDT has been used in clinics for many years, there is limited information on the feasibility and therapeutic efficacy in the treatment of COVID-19. Because of the high safety profile, PDT should be tested in patients at different stages of COVID-19. There are many types of PSs and photons that have a variety of outcomes and targets. It is important to test which PS and light are feasible and effective at inactivating the SARS-CoV-2 virus, in particular, some PS and photons that are effective at inactivating RNA viruses and microbial pathogens. A combination of PDT with PBM might be valuable, especially by combining different PSs. New advances in PDT might be discovered to control the spread of the SARS-CoV-2 virus and the COVID-19 pandemic.

**Conclusions**

PDT is a safe, cost-effective, and easy to handle therapy without obvious side effects. PDT is target specific and unlikely to induce resistance in the SARS-CoV-2 virus. An intravenous approach for a light source and PS might be feasible, and PDT might be a potential rapidly applicable therapy for intervention in COVID-19 patients in the clinic.
Acknowledgments

Author contributions

Study design (MQ), searching the databases and extracting the data (RT, UAK, SK), analysis and interpretation of data (RT, UAK, SK, FA), drafting the manuscript (RT, UAK, SK, MQ), critically revising the manuscript (MQ, RT, UAK, FA). All authors contributed to the final version of the manuscript.

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