Journal of Exploratory Research in Pharmacology **2021** vol. 6(2) | 44–52
DOI: 10.14218/JERP.2020.00036

Review Article

Photodynamic Therapy: A Rational Approach Toward COVID-19 Management

Roha Tariq[1†], Usama Ahmed Khalid[2†], Samra Kanwal[3], Fazal Adnan[4] and Muhammad Qasim[5*]

[1]Department of Biotechnology, Lahore College for Women University, Lahore, Punjab, Pakistan; [2]Department of Biotechnology & Genetic Engineering, Kohat University of Science and Technology, Kohat, Khyber Pakhtunkhwa, Pakistan; [3]Institute of Biochemistry and Biotechnology, University of the Punjab, Lahore, Pakistan; [4]Atta-Ur-Rehman School of Applied Biosciences, National University of Science and Technology Islamabad, Pakistan; [5]Department of Microbiology, Kohat University of Science and Technology, Kohat, 26000, Khyber Pakhtunkhwa, Pakistan

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.[1] Then, gene sequencing identified that COVID-19 was caused by an enveloped RNA Beta-coronavirus,[2] 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 of SARS that was reported in 2002.[3,4]

In February 2021, there were >100 million people with SARS-CoV-2 virus infection and >2.2 million COVID-19 patients had died worldwide. The US and Europe share the maximum burden of this pandemic, which accounts for 85% of new cases and 86% of new deaths globally.[5] In many countries, the death rate is increasing due to severe lungs damage and relevant multiple organ failure syndromes.[6,7]

COVID-19 is highly transmissible, especially in immune-compromised individuals and older people with preexisting chronic diseases, such as diabetes, cardiovascular diseases, hypertension, and any terminal cancers.[8] 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.[9] Case-fatality rate increases with age.[10,11] 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

Keywords: Photodynamic inactivation; COVID-19; Novel treatment; Antiviral therapy.
Abbreviations: COVID-19, coronavirus disease 2019; MB, methylene blue; mRNA, messenger ribonucleic acid; PBM, photobiomodulation; PDT, photodynamic therapy; PS, photosensitizer; ROS, reactive oxygen species; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SDT, sonodynamic therapy.
***Correspondence to:** Muhammad Qasim, Department of Microbiology, Kohat University of Science and Technology, Kohat, 26000, Khyber Pakhtunkhwa, Pakistan. ORCID: http://orcid.org/0000-0002-1472-7150. Tel: +92 313 6318 868, Email: qasim89@gmail.com
†Co-first authorship: Contributed equally to this work.
How to cite this article: Tariq R, Khalid UA, Kanwal S, Adnan F, Qasim M. Photodynamic Therapy: A Rational Approach toward COVID-19 Management. *J Explor Res Pharmacol* 2021;6(2):44–52. doi: 10.14218/JERP.2020.00036.

strategies for COVID-19 include the inhibition of SARS-CoV-2 replication and inflammation to limit tissue damages.[12] The drugs include antiviral drugs, Veklury (remdesivir), Favipiravir, Arbidol, Janus Kinase (JAK) inhibitor, Baricitinib (Olumiant), and convalescent plasma for hospitalized COVID-19 patients.[13,14] Second, monoclonal antibodies, such as bamlanivimab, casirivimab, and imdevimab have been approved for emergency use for severe COVID-19 patients.[15] Other treatments, such as autophagy inhibitor chloroquinine, anti-inflammatory dexamethasone, and methylprednisolone, have been used in clinics.[16]

Recently, out of 52 potential vaccine candidates two vaccines, BNT162b2 from Pfizer/BioNTech and mRNA-1273 from Moderna have received Emergency Use Authorization from the FDA and other vaccines are in clinical Phase 3 trials.[17,18] Two COVID-19 mRNA vaccines, BNT162b2 and mRNA-1273, have been approved for use in patients aged ≥18 years.[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.[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 cautions against using them for the treatment of COVID-19 patients due to their potential cardiac side effects, including QT prolongation, ventricular arrhythmias, and cardiac toxicity.[22–24] In addition, corticosteroid types of drugs for COVID-19 might increase lung injury.[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,[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.[28] PDT is a unique technique to kill various pathogens, including bacteria, fungi, viruses, and parasites.[29] Therefore, PDT is called photodynamic antimicrobial chemotherapy (PACT) and photodynamic inactivation (PDI).[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.[32] Then, in 1930 this therapy was shown to display antiviral activity.[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.[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 ($^1O_2$). 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.[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.[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.[42] Therefore, the characteristics of PS and light are important in PDT to treat a variety of diseases, which depends on the causative agents.[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.[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.[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.[47,48] Chlorophyll derivatives, curcumin, vitamin B2, methylene blue (MB), and porphyrins have been used as PS.[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.[52] In contrast, UV-VIS excite most clinically approved PSs.[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.[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.[51] Lasers, such as argon, quartz halogen, and xenon, are efficient at 488–514 nm, 620–640 nm, and 600–700 nm, respectively.[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 aeruginosa,* respectively.[57–60]

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.[61] 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.[62] 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.[63] 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),[64] keratitis (ocular), as well as Herpes zoster infection.[65,66] In addition, PDT is effective for HPV infection-induced laryngeal papillomata using dihematoporphyrin ether and hematoporphyrin derivative.[67] 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,[68] 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.[69] PDT has been used to treat eye disorders and dermatological diseases in India, Egypt, and China for many years.[70] Recently, PDT has been used in several localized microbial infections, in particular, for multidrug-resistant microbes due to its rapid efficacy.[71,72] 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.[73,74] 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.[75] 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.[76]

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 HSV-1 and bacteriophage M13 with distinct concentrations in response to varying intensities of light.[77–79] MB is involved in RNA and enveloped protein damage in various viruses, such as human immunodeficiency virus (HIV) and vesicular stomatitis virus.[77,80] Many radicals have different results, Type 1 radicals target sugar moieties, for instance, singlet oxygen is sensitive to the guanine nucleotide.[81] MB and riboflavin inactivate coronaviruses and might target SARS-CoV-2. Ruthenium and osmium-based compounds are activated by light in the range of 400–675 nm and selectively destroy different types of tumor cells.[82] The action of different PS components with respective viral molecular targets is given in Table 1.[50,61,77–81,83–92]

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.[93] Due to the spread of COVID-19, researchers are developing new therapies to fight it.[94] Some treatments and medicines have shown promising outcomes in clinical trials and have been approved for clinical applications to combat SARS-CoV-2.[95] Of interest, a recent study suggested PDT as an alternative therapy for SARS-CoV-2 infection in 2020.[51] 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.[96] A previous study demonstrated that PDT inactivates SARS-CoV.[97] 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.[98,99]

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.[100] ROS targets the guanine nucleotide to inhibit viral replication.[79] The activated PS could easily target cysteine, L-histidine, tyrosine, methionine, and tryptophan to change their associated protein structure and functions.[101,102] The hydroxyl group and singlet oxygen radical react differently to their targets. The singlet oxygen reacts more efficiently on viruses than other radicals,[103] and effectively targets guanine residues and tyrosine; histidine and tryptophan.[83,93] 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 inactivate coronaviruses.[84,85] Schikora *et al.*[104] 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.[49] An intravenous approach with blue light might be efficient using green-based PS, such as indocyanine.[51] 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.[105] 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.[106] 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.[105,107–111] 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

DOI: 10.14218/JERP.2020.00036 | Volume 6 Issue 2, June 2021

Table 1. The potential targets of PDT against different viruses, and the PDT components with their respective molecular viral targets are shown with respect to their mechanisms of action

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 fusion 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	Merocyanine 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.

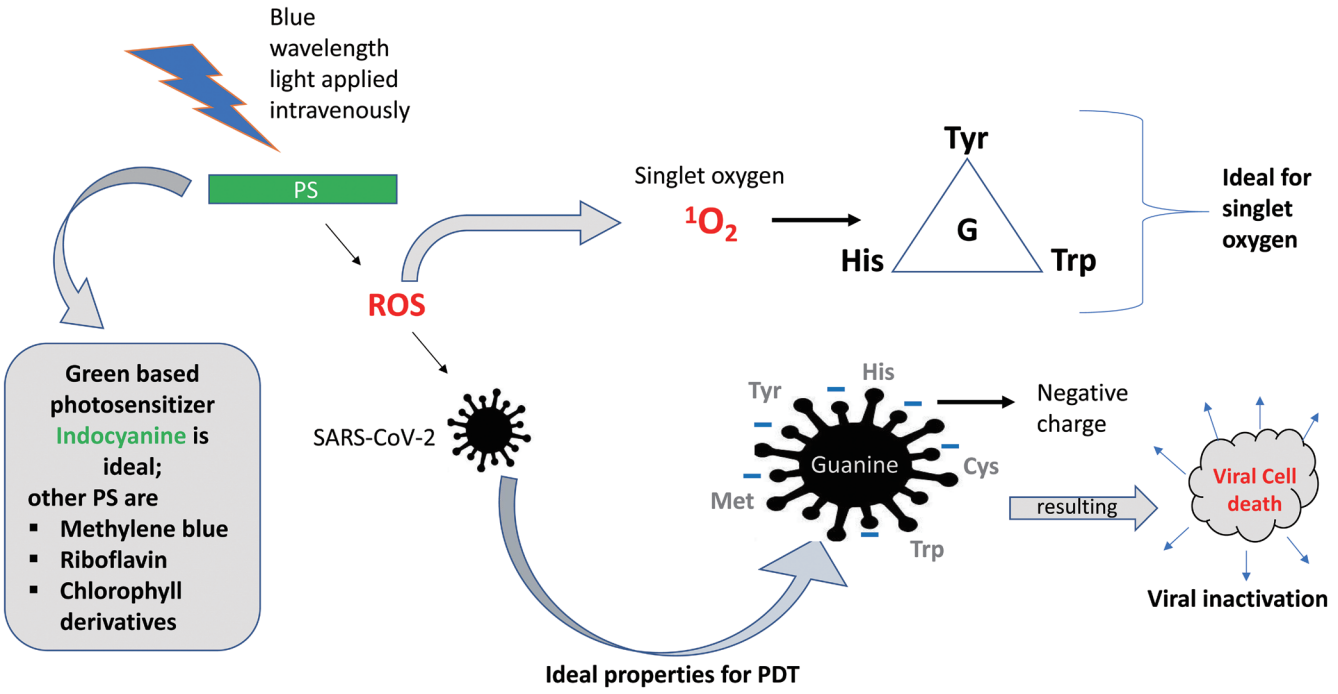

Fig. 1. Thematic diagram of PDT for COVID-19 therapy. This diagram was designed based on various published studies, which suggested the ideal conditions of the PDT for COVID-19 therapy. Enveloped protein negatively charged biomolecules, guanine residues, and five amino acids (tyrosine, histidine, tryptophan, cysteine, and methionine), are ideal properties of viruses that are present in SARS-CoV-2. In addition, singlet oxygen could be a good radical against SARS-CoV-2 because it is destructive towards guanine residues and histidine, tryptophan, and tyrosine amino acids. Fekrazad (2020) suggested the use of blue wavelength light with green-based photosensitizer indocyanine for COVID-19 therapy.[51] All these actions result in cell death. PDT, photodynamic therapy; PS, photosensitizer; ROS, reactive oxygen species.

deep tissues to irradiate sensitizer molecules.[112] In addition, ultrasound causes the poration phenomenon of the cell membrane, termed sonoporation.[113] Previous studies have shown that SDT combined with PS, such as porphyrin xantene, TiO_2, and fluoroquinolone antibiotics, effectively inactivate bacteria.[114,115] Other data indicates that SDT eradicates bacteria, viruses, parasites, and other microbial entities.[112] 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.[7,116] 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.[117] PDT can be carried out by the nebulization of PS into the respiratory tract or by using a catheter to deliver light.[118] Many groups are establishing a PDT protocol for the treatment of COVID-19[119] as PDT inactivates other virus-related respiratory diseases,[120] and an RNA virus is also more sensitive to PDT inactivation.[121,122] Recently, a study reported the successful use of PDT in the disinfection of oral and nasal cavities in patients with early-stage COVID-19.[104] 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

None.

Funding

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

Conflict of interest

We declare no conflicts of interest.

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.

References

[1] Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, *et al*. A new coronavirus associated with human respiratory disease in China. Nature 2020;579(7798):265–269. doi:10.1038/s41586-020-2008-3.
[2] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, *et al*. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395(10224):565–574. doi:10.1016/S0140-6736(20)30251-8.
[3] Zhao L, Jha BK, Wu A, Elliott R, Ziebuhr J, Gorbalenya AE, *et al*. Antagonism of the interferon-induced OAS-RNase L pathway by murine coronavirus ns2 protein is required for virus replication and liver pathology. Cell Host Microbe 2012;11(6):607–616. doi:10.1016/j.chom.2012.04.011.
[4] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. New Engl J Med 2020;382(8):727–733. doi:10.1056/NEJMoa2001017.
[5] WHO. COVID-19 Weekly Epidemiological Update. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update---2-february-2021. Accessed February 5, 2021.
[6] Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, *et al*. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395(10223):514–523. doi:10.1016/S0140-6736(20)30154-9.
[7] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497–506. doi:10.1016/S0140-6736(20)30183-5.
[8] Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, *et al*. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr 2020;16(3):223–231. doi:10.1007/s12519-020-00343-7.
[9] Le Couteur DG, Anderson RM, Newman AB. COVID-19 Through the Lens of Gerontology. J Gerontol A Biol Sci Med Sci 2020;75(9):e119–e120. doi:10.1093/gerona/glaa077.
[10] National Governors Association. Roadmap to Recovery: A Public Health Guide for Governors [updated: April 21, 2020]. Available from: https://www.nga.org/wp-content/uploads/2020/04/NGA-Report.pdf?wpisrc=nl_health202. Accessed November 04, 2021.
[11] Livingston E, Bucher K. Coronavirus disease 2019 (COVID-19) in Italy. JAMA 2020;323(14):1335. doi:10.1001/jama.2020.4344.
[12] Iyer M, Jayaramayya K, Subramaniam MD, Lee SB, Dayem AA, Cho SG, *et al*. COVID-19: an update on diagnostic and therapeutic approaches. BMB Rep 2020;53(4):191. doi:10.5483/BMBRep.2020.53.4.080.
[13] Xu J, Xue Y, Zhou R, Shi PY, Li H, Zhou J. Drug repurposing approach to combating coronavirus: Potential drugs and drug targets. Med Res Rev 2020. doi:10.1002/med.21763.
[14] Abolghasemi H, Eshghi P, Cheraghali AM, Fooladi AA, Moghaddam FB, Imanizadeh S, *et al*. Clinical efficacy of convalescent plasma for treatment of COVID-19 infections: Results of a multicenter clinical study. Transfus Apher Sci 2020;59(5):102875. doi:10.1016/j.transci.2020.102875.
[15] Global Virus Network. Progress in the Treatments of COVID-19 [updated: November 25, 2020]. https://gvn.org/progress-in-the-treatments-of-covid-19/. Accessed December 30, 2020.
[16] Harrison C. Coronavirus puts drug repurposing on the fast track. Nat Biotechnol 2020;38(4):379–381. doi:10.1038/d41587-020-00003-1.
[17] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, *et al*. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med 2020;383(27):2603–2615. doi:10.1056/NEJMoa2034577.
[18] Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, *et al*. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med 2020;383(25):2427–2438. doi:10.1056/NEJMoa2028436.
[19] De Soto JA. Evaluation of the Moderna, Pfizer/biontech, Astrazeneca/oxford and Sputnik V Vaccines for COVID-19. OSF Preprints 2020. doi:10.31219/osf.io/e4rqu.
[20] Li Q, Lu H. Latest updates on COVID-19 vaccines. BioSci Trend 2021;14(6):463–466. doi:10.5582/bst.2020.03445.
[21] Poland GA, Ovsyannikova IG, Kennedy RB. SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. Lancet 2020;396(10262):1595–1606. doi:10.1016/S0140-6736(20)32137-1.
[22] Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, *et al*. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agent 2020;56(1):105949. doi:10.1016/j.ijantimicag.2020.105949.
[23] Jorge A. Hydroxychloroquine in the prevention of COVID-19 mortality. Lancet Rheum 2021;3(1):e2–3. doi:10.1016/S2665-9913(20)30390-8.
[24] Yazdany J, Kim AHJ. Use of hydroxychloroquine and chloroquine during the COVID-19 pandemic: what every clinician should know. Ann Intern Med 2020;172(11):754–755. doi:10.7326/M20-1334.
[25] Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395(10223):473–475. doi:10.1016/S0140-6736(20)30317-2.
[26] Shang L, Zhao J, Hu Y, Du R, Cao B. On the use of corticosteroids for 2019-nCoV pneumonia. Lancet 2020;395(10225):683. doi:10.1016/S0140-6736(20)30361-5.
[27] Pillaiyar T, Meenakshisundaram S, Manickam M. Recent discovery and development of inhibitors targeting coronaviruses. Drug Discov Today 2020;25(4):668–688. doi:10.1016/j.drudis.2020.01.015.
[28] Abrahamse H, Hamblin MR. Photomedicine and stem cells: the Janus face of photodynamic therapy (PDT) to kill cancer stem cells, and photobiomodulation (PBM) to stimulate normal stem cells. Morgan & Claypool Publishers; 2017.
[29] Wainwright M, Maisch T, Nonell S, Plaetzer K, Almeida A, Tegos GP, *et al*. Photoantimicrobials—are we afraid of the light? Lancet Infect Dis 2017;17(2):e49–e55. doi:10.1016/S1473-3099(16)30268-7.
[30] Awad MM, Tovmasyan A, Craik JD, Batinic-Haberle I, Benov LT. Important cellular targets for antimicrobial photodynamic therapy. Appl Microbiol Biotechnol 2016;100(17):7679–7688. doi:10.1007/s00253-016-7632-3.
[31] Hamblin MR. Antimicrobial photodynamic inactivation: a bright new technique to kill resistant microbes. Curr Opin Microbiol 2016;33:67–73. doi:10.1016/j.mib.2016.06.008.
[32] Raab O. Uber die Wirkung, fluorescirender Stoffe auf infusorien. Z Biol 1900;39:524–546.
[33] Perdrau JR, Todd C. The photodynamic action of methylene blue on certain viruses. Proc Roy Soc Lond 1933;112(777):288–298. doi:10.1098/rspb.1933.0011.
[34] Schultz EW. Inactivation of Staphyloccus Bacteriophage by Methylene Blue. Proc Soc Exp Biol Med 1928;26(2):100–101. doi:10.3181/00379727-26-4158.
[35] DeRosa MC, Crutchley RJ. Photosensitized singlet oxygen and its ap-

plications. Coord Chem Rev 2002;233:351–71. doi:10.1016/S0010-8545(02)00034-6.
[36] Broekgaarden M, Weijer R, van Gulik TM, Hamblin MR, Heger M. Tumor cell survival pathways activated by photodynamic therapy: a molecular basis for pharmacological inhibition strategies. Cancer Metastasis Rev 2015;34(4):643–690. doi:10.1007/s10555-015-9588-7.
[37] Mahmoudi H, Bahador A, Pourhajibagher M, Alikhani MY. Antimicrobial Photodynamic Therapy: An Effective Alternative Approach to Control Bacterial Infections. J Lasers Med Sci 2018;9(3):154–160. doi:10.15171/jlms.2018.29.
[38] Capella MA, Capella LS. A light in multidrug resistance: photodynamic treatment of multidrug-resistant tumors. J Biomed Sci 2003;10(4):361–366. doi:10.1159/000071155.
[39] Castano AP, Demidova TN, Hamblin MR. Mechanisms in photodynamic therapy: part one—photosensitizers, photochemistry and cellular localization. Photodiagn Photodyn Ther 2004;1(4):279–293. doi:10.1016/S1572-1000(05)00007-4.
[40] Costa L, Carvalho CM, Faustino MA, Neves MG, Tomé JP, Tomé AC, *et al*. Sewage bacteriophage inactivation by cationic porphyrins: influence of light parameters. Photochem Photobiol Sci 2010;9(8):1126–1133. doi:10.1039/C0PP00051E.
[41] Prates RA, da Silva EG, Yomada AM Jr, Suzuki LC, Paula CR, Ribeiro MS. Light parameters influence cell viability in antifungal photodynamic therapy in a fluence and rate fluence dependent manner. Laser Phys 2009;19:1038–1044. doi:10.1134/S1054660X09050284.
[42] Antognazza MR, Abdel Aziz I, Lodola F. Use of exogenous and endogenous photomediators as efficient ROS modulation tools: Results and perspectives for therapeutic purposes. Oxid Med Cell Longev 2019;2019:2867516. doi:10.1155/2019/2867516.
[43] Plotino G, Grande NM, Mercade M. Photodynamic therapy in endodontics. Int Endod J 2019;52(6):760–774. doi:10.1111/iej.13057.
[44] Fekrazad R, Nejat A, Kalhori KA. Antimicrobial photodynamic therapy with nanoparticles versus conventional photosensitizer in oral diseases. Nanostructures Antimicrobial Ther 2017;237–259. doi:10.1016/B978-0-323-46152-8.00010-X.
[45] Sharma SK, Mroz P, Dai T, Huang YY, Denis TG, Hamblin MR. Photodynamic therapy for cancer and for infections: what is the difference? Isr J Chem 2012;52(8-9):691–705. doi:10.1002/ijch.201100062.
[46] Yin R, Hamblin MR. Antimicrobial photosensitizers: drug discovery under the spotlight. Curr Med Chem 2015;22(18):2159–2185. doi:10.2174/0929867322666150319120134.
[47] Agostinis P, Berg K, Cengel KA, Foster TH, Girotti AW, Gollnick SO, *et al*. Photodynamic therapy of cancer: an update. CA Cancer J Clin 2011;61(4):250–281. doi:10.3322/caac.20114.
[48] Gad F, Zahra T, Francis KP, Hasan T, Hamblin MR. Targeted photodynamic therapy of established soft-tissue infections in mice. Photochem Photobiol Sci 2004;3(5):451–458. doi:10.1039/B311901G.
[49] Almeida A, Cunha A, Faustino MA, Tomé AC, Neves MG. Porphyrins as antimicrobial photosensitizing agents. Photodynamic inactivation of microbial pathogens: medical and environmental applications. R Soc Chem 2011;11:83–160. doi:10.1039/9781849733083-00083.
[50] Caminos DA, Durantini EN. Interaction and photodynamic activity of cationic porphyrin derivatives bearing different patterns of charge distribution with GMP and DNA. J Photochem Photobiol A Chem 2008;198(2-3):274–281. doi:10.1016/j.jphotochem.2008.04.005.
[51] Fekrazad R. Photobiomodulation and antiviral photodynamic therapy as a possible novel approach in COVID-19 management. Photobiomod Photomed Laser Surg 2020;38(5):255–257. doi:10.1089/photob.2020.4868.
[52] Pawlicki M, Collins HA, Denning RG, Anderson HL. Two-photon absorption and the design of two-photon dyes. Angewandte Chemie Int Ed 2009;48(18):3244–3266. doi:10.1002/anie.200805257.
[53] Zhao J, Duan L, Wang A, Fei J, Li J. Insight into the efficiency of oxygen introduced photodynamic therapy (PDT) and deep PDT against cancers with various assembled nanocarriers. Nanomed Nanobiotechnol 2020;12(1):e1583. doi:10.1002/wnan.1583.
[54] Brancaleon L, Moseley H. Laser and non-laser light sources for photodynamic therapy. Laser Med Sci 2002;17(3):173–186. doi:10.1007/s101030200027.
[55] Juzeniene A, Juzenas P, Ma LW, Iani V, Moan J. Effectiveness of different light sources for 5-aminolevulinic acid photodynamic therapy. J Laser Med Sci 2004;19(3):139–149. doi:10.1007/s10103-004-0314-x.
[56] Wainwright M. Local treatment of viral disease using photodynamic therapy. Int J Antimicrob Agents 2003;21(6):510–520. doi:10.1016/S0924-8579(03)00035-9.
[57] Almeida J, Tomé JP, Neves MG, Tomé AC, Cavaleiro JA, Cunha Â, *et al*. Photodynamic inactivation of multidrug-resistant bacteria in hospital wastewaters: influence of residual antibiotics. Photochem Photobiol Sci 2014;13(4):626–633. doi:10.1039/c3pp50195g.
[58] Choi S, Lee H, Yu J, Chae H. In vitro augmented photodynamic bactericidal activity of tetracycline and chitosan against Clostridium difficile KCTC5009 in the planktonic cultures. J Photochem Photobiol B 2015;153:7–12. doi:10.1016/j.jphotobiol.2015.09.003.
[59] Oppezzo OJ, Forte Giacobone AF. Lethal effect of photodynamic treatment on persister bacteria. Photochem Photobiol 2018;94(1):186–189. doi:10.1111/php.12843.
[60] Pereira NLF, Aquino PEA, Júnior JGAS, Cristo JS, Vieira Filho MA, Moura FF, *et al*. Antibacterial activity and antibiotic modulating potential of the essential oil obtained from Eugenia jambolana in association with led lights. J Photochem Photobiol B 2017;174:144–149. doi:10.1016/j.jphotobiol.2017.07.027.
[61] Lim ME, Lee YL, Zhang Y, Chu JJ. Photodynamic inactivation of viruses using upconversion nanoparticles. Biomaterials 2012;33(6):1912–1920. doi:10.1016/j.biomaterials.2011.11.033.
[62] Wiehe A, O'Brien JM, Senge MO. Trends and targets in antiviral phototherapy. Photochem Photobiol Sci 2019;18(11):2565–2612. doi:10.1039/C9PP00211A.
[63] Zhao B, He YY. Recent advances in the prevention and treatment of skin cancer using photodynamic therapy. Expert Rev Anticancer Ther 2010;10(11):1797–1809. doi:10.1586/era.10.154.
[64] Marotti J, Aranha ACC, Eduardo CDP, Ribeiro MS. Photodynamic therapy can be effective as a treatment for herpes simplex labialis. Photomed Laser Surg 2009;27(2):357–363. doi:10.1089/pho.2008.2268.
[65] Halili F, Arboleda A, Durkee H, Taneja M, Miller D, Alawa KA, *et al*. Rose bengal–and riboflavin-mediated photodynamic therapy to inhibit methicillin-resistant Staphylococcus aureus keratitis isolates. Am J Opthamol 2016;166:194–202. doi:10.1016/j.ajo.2016.03.014.
[66] Teitelbaum S, Azevedo LH, Bernaola-Paredes WE. Antimicrobial Photodynamic Therapy Used as First Choice to Treat Herpes Zoster Virus Infection in Younger Patient: A Case Report. Photobiomodul Photomed Laser Surg 2020;38(4):232–236. doi:10.1089/photob.2019.4725.
[67] Frisch S, Guo AM. Diagnostic methods and management strategies of herpes simplex and herpes zoster infections. Clin Geriatr Med 2013;29(2):501–526. doi:10.1016/j.cger.2013.01.003.
[68] Dai T, Huang YY, Hamblin MR. Photodynamic therapy for localized infections—state of the art. Photodiagn Photodyn Ther 2009;6(3-4):170–188. doi:10.1016/j.pdpdt.2009.10.008.
[69] Hale JD, Hancock RE. Alternative mechanisms of action of cationic antimicrobial peptides on bacteria. Expert Rev Anti Infect Ther 2007;5(6):951–959. doi:10.1586/14787210.5.6.951.
[70] Castano AP, Mroz P, Hamblin MR. Photodynamic therapy and anti-tumour immunity. Nat Rev Cancer 2006;6(7):535–545. doi:10.1038/nrc1894.
[71] Rodríguez Amigo B. Light-sensitive nanocarriers for drug delivery in photodynamic therapy. Universtat Ramon Llull [updated: February 09, 2018]. Available from: https://www.tdx.cat/handle/10803/462210. Accessed October 29, 2020.
[72] Cieplik F, Deng D, Crielaard W, Buchalla W, Hellwig E, Al-Ahmad A, *et al*. Antimicrobial photodynamic therapy–what we know and what we don't. Crit Rev Microbiol 2018;44(5):571–589. doi:10.1080/1040841X.2018.1467876.
[73] Pérez-Laguna V, García-Malinis AJ, Aspiroz C, Rezusta A, Gilaberte Y. Antimicrobial effects of photodynamic therapy. G Ital Dermatol Venereol 2018;153(6):833–846. doi:10.23736/S0392-0488.18.06007-8.
[74] Kikuchi T, Mogi M, Okabe I, Okada K, Goto H, Sasaki Y, *et al*. Adjunctive application of antimicrobial photodynamic therapy in non-surgical periodontal treatment: a review of literature. Int J Mol Sci 2015;16(10):24111–24126. doi:10.3390/ijms161024111.
[75] de Melo WC, Avci P, de Oliveira MN, Gupta A, Vecchio D, Sadasivam M, *et al*. Photodynamic inactivation of biofilm: taking a lightly colored approach to stubborn infection. Expert Rev Anti Infect

2013;11(7):669–693. doi:10.1586/14787210.2013.811861.
[76] Siddiqui AR, Bernstein JM. Chronic wound infection: facts and controversies. Clin Dermatol 2010;28(5):519–526. doi:10.1016/j.clindermatol.2010.03.009.
[77] Abe H, Wagner SJ. Analysis of viral DNA, protein and envelope damage after methylene blue, phthalocyanine derivative or merocyanine 540 photosensitization. Photochem Photobiol 1995;61(4):402–409. doi:10.1111/j.1751-1097.1995.tb08630.x.
[78] Müller-Breitkreutz K, Mohr H. Infection cycle of herpes viruses after photodynamic treatment with methylene blue and light. Beitr Infusionsther Transfusionsmed 1997;34:37–42.
[79] Wainwright M. Methylene blue derivatives-suitable photoantimicrobials for blood product disinfection? Int J Antimicrob Agents 2000;16(4):381–394. doi:10.1016/S0924-8579(00)00207-7.
[80] Bachmann B, Knüver-Hopf J, Lambrecht B, Mohr H. Target structures for HIV-1 inactivation by methylene blue and light. J Med Virol 1995;47(2):172–178. doi:10.1002/jmv.1890470211.
[81] Wainwright M. Photodynamic antimicrobial chemotherapy (PACT). J Antimicrob Chemother 1998;42(1):13–28. doi:10.1093/jac/42.1.13.
[82] Carlsen L, Mandeville T, Barrett P, Bradner E, Sainuddin T, McFarland S, *et al*. Novel metal-based photosensitizers for photodynamic therapy: exploratory study (Conference Presentation), Proc. SPIE 11070, 17th International Photodynamic Association World Congress, 110701U (14 August 2019); https://doi.org/10.1117/12.2526180.
[83] Baker A, Kanofsky JR. Quenching of singlet oxygen by biomolecules from L1210 leukemia cells. Photochem Photobiol 1992;55(4):523–528. doi:10.1111/j.1751-1097.1992.tb04273.x.
[84] Keil SD, Bowen R, Marschner S. Inactivation of Middle East respiratory syndrome coronavirus (MERS-C o V) in plasma products using a riboflavin-based and ultraviolet light-based photochemical treatment. Transfusion 2016;56(12):2948–2952. doi:10.1111/trf.13860.
[85] Ruane PH, Edrich R, Gampp D, Keil SD, Leonard RL, Goodrich RP. Photochemical inactivation of selected viruses and bacteria in platelet concentrates using riboflavin and light. Transfusion 2004;44(6):877–885. doi:10.1111/j.1537-2995.2004.03355.x.
[86] Moor AC, Gompel AE, Brand A, Dubbelman TM, VanSteveninck J. Primary targets for photoinactivation of vesicular stomatitis virus by AIPcS4 or Pc4 and red light. J Photochem Photobiol 1997;65(3):465–470. doi:10.1111/j.1751-1097.1997.tb08591.x.
[87] Schneider JE Jr, Tabatabaie T, Maidt L, Smith RH, Nguyen X, Pye Q, *et al*. Potential mechanisms of photodynamic inactivation of virus by methylene blue I. RNA–protein crosslinks and other oxidative lesions in Qβ Bacteriophage. Photochem Photobiol 1998;67(3):350–357. doi:10.1111/j.1751-1097.1998.tb05209.x.
[88] Smetana Z, Ben-Hur E, Mendelson E, Salzberg S, Wagner P, Malik Z. Herpes simplex virus proteins are damaged following photodynamic inactivation with phthalocyanines. J Photochem Photobiol B 1998;44(1):77–83. doi:10.1016/S1011-1344(98)00124-9.
[89] Vzorov AN, Dixon DW, Trommel JS, Marzilli LG, Compans RW. Inactivation of human immunodeficiency virus type 1 by porphyrins. Antimicrob Agent Chemother 2002;46(12):3917–3925. doi:10.1128/AAC.46.12.3917-3925.2002.
[90] Turner GS, Kaplan C. Photoinactivation of vaccinia virus with rose bengal. J Gen Virol 1968;3(3):433–443. doi:10.1099/0022-1317-3-3-433.
[91] Lenard J, Rabson A, Vanderoef R. Photodynamic inactivation of infectivity of human immunodeficiency virus and other enveloped viruses using hypericin and rose bengal: inhibition of fusion and syncytia formation. PNAS 1993;90(1):158–162. doi:10.1073/pnas.90.1.158.
[92] Lee M, Lee Y. Anti-retroviral effect of chlorophyll derivatives (CpD-D) by photosensitization. Yonsei Med J 1990;31(4):339–346. doi:10.3349/ymj.1990.31.4.339.
[93] Borgia F, Giuffrida R, Caradonna E, Vaccaro M, Guarneri F, Cannavò SP. Early and late onset side effects of photodynamic therapy. Biomed 2018;6(1):12. doi:10.3390/biomedicines6010012.
[94] Liu C, Zhou Q, Li Y, Garner LV, Watkins SP, Carter LJ, *et al*. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. ACS Cent Sci 2020;6(3):315–331. doi:10.1021/acscentsci.0c00272.
[95] Dhama K, Sharun K, Tiwari R, Dadar M, Malik YS, Singh KP, *et al*. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Hum Vaccines Immunother 2020;16(6):1232–1238. doi:10.1080/21645515.2020.1735227.
[96] Käsermann F, Kempf C. Photodynamic inactivation of enveloped viruses by buckminsterfullerene. Antivir Res 1997;34(1):65–70. doi:10.1016/S0166-3542(96)01207-7.
[97] Eickmann M, Gravemann U, Handke W, Tolksdorf F, Reichenberg S, Müller TH, *et al*. Inactivation of three emerging viruses–severe acute respiratory syndrome coronavirus, Crimean–Congo haemorrhagic fever virus and Nipah virus–in platelet concentrates by ultraviolet C light and in plasma by methylene blue plus visible light. Vox Sang 2020;115(3):146–1451. doi:10.1111/vox.12888.
[98] Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, *et al*. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microb Infect 2020;9(1):221–236. doi:10.1080/22221751.2020.1719902.
[99] Astuti I, Ysrafil. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes Metab Syndr 2020;14(4):407–412. doi:10.1016/j.dsx.2020.04.020.
[100] Robertson EG, Simons JP. Getting into shape: conformational and supramolecular landscapes in small biomolecules and their hydrated clusters. Phys Chem Chem Phys 2001;3(1):1–18. doi:10.1039/B008225M.
[101] Girotti AW. Photodynamic action of protoporphyrin IX on human erythrocytes: cross-linking of membrane proteins. Biochemical Biophys Res Comm 1976;72(4):1367–1374. doi:10.1016/S0006-291X(76)80165-9.
[102] Macdonald IJ, Dougherty TJ. Basic principles of photodynamic therapy. J Porphyrins Phthalocyanines 2001;5(02):105–129. doi:10.1002/jpp.328.
[103] Costa L, Tomé JP, Neves MG, Tomé AC, Cavaleiro JA, Cunha Â, *et al*. Susceptibility of non-enveloped DNA-and RNA-type viruses to photodynamic inactivation. Photochem Photobiol Sci 2012;11(10):1520–1523. doi:10.1039/C2PP25156F.
[104] Schikora D, Hepburn J, Plavin SR. Reduction of the viral load by non-invasive photodynamic therapy in early stages of COVID-19 infection. Am J Virol Dis 2020;2(1):1–5.
[105] Ye Q, Wang B, Mao J. The pathogenesis and treatment of theCytokine Storm'in COVID-19. J Infect 2020;80(6):607–613. doi:10.1016/j.jinf.2020.03.037.
[106] Thompson MR, Kaminski JJ, Kurt-Jones EA, Fitzgerald KA. Pattern recognition receptors and the innate immune response to viral infection. Viruses 2011;3(6):920–940. doi:10.3390/v3060920.
[107] Ragab D, Salah Eldin H, Taeimah M, Khattab R, Salem R. The COVID-19 cytokine storm; what we know so far. Front Immunol 2020;11:1446. doi:10.3389/fimmu.2020.01446.
[108] Auyeung TW, Lee JS, Lai WK, Choi CH, Lee HK, Lee JS, *et al*. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. J Infect 2005;51(2):98–102. doi:10.1016/j.jinf.2004.09.008.
[109] Chen WH, Strych U, Hotez PJ, Bottazzi ME. The SARS-CoV-2 vaccine pipeline: an overview. Curr Trop Med Rep 2020;7:61–64. doi:10.1007/s40475-020-00201-6.
[110] Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trend 2020;14(1):72–73. doi:10.5582/bst.2020.01047.
[111] Ju M, He H, Chen S, Liu Y, Liu Y, Pan S, *et al*. Ulinastatin ameliorates LPS-induced pulmonary inflammation and injury by blocking the MAPK/NF-κB signaling pathways in rats. Mol Med Rep 2019;20(4):3347–3354. doi:10.3892/mmr.2019.10561.
[112] Ma X, Pan H, Wu G, Yang Z, Yi J. Ultrasound may be exploited for the treatment of microbial diseases. J Med hypotheses 2009;73(1):18–19. doi:10.1016/j.mehy.2009.01.033.
[113] Nomikou N, Li YS, McHale AP. Ultrasound-enhanced drug dispersion through solid tumours and its possible role in aiding ultrasound-targeted cancer chemotherapy. Cancer Lett 2010;288(1):94–98. doi:10.1016/j.canlet.2009.06.028.
[114] Harris F, Dennison SR, Phoenix DA. Sounding the death knell for microbes? Trends Mol Med 2014;20(7):363–367. doi:10.1016/j.molmed.2014.05.005.

[115] Harris F, Dennison SR, Phoenix DA. Using sound for microbial eradication–light at the end of the tunnel? FEMS Microbil Lett 2014;356(1):20–22. doi:10.1111/1574-6968.12484.
[116] Hu X, Huang YY, Wang Y, Wang X, Hamblin MR. Antimicrobial photodynamic therapy to control clinically relevant biofilm infections. Front Microbiol 2018;9:1299. doi:10.3389/fmicb.2018.01299.
[117] Blanco KC, Inada NM, Carbinatto FM, Giusti AL, Bagnato VS. Treatment of recurrent pharyngotonsillitis by photodynamic therapy. Photodiagn Photodyn 2017;18:138–139. doi:10.1016/j.pdpdt.2017.01.187.
[118] Kassab G, Geralde MC, Inada NM, Achiles AE, Guerra VG, Bagnato VS. Nebulization as a tool for photosensitizer delivery to the respiratory tract. J Biophoton 2019;12(4):e201800189. doi:10.1002/jbio.201800189.
[119] Moghissi K, Dixon K, Gibbins S. Does PDT have potential in the treatment of COVID 19 patients? Photodiagn Photodyn Ther 2020;31:101889. doi:10.1016/j.pdpdt.2020.101889.
[120] Kurman JS, Pastis NJ, Murgu SD. Photodynamic Therapy and Its Use in Lung Disease. Curr Pulmnol Rep 2019;8(4):215–221. doi:10.1007/s13665-019-00241-y.
[121] Costa L, Faustino MA, Neves MG, Cunha Â, Almeida A. Photodynamic inactivation of mammalian viruses and bacteriophages. Viruses 2012;4(7):1034–1074. doi:10.3390/v4071034.
[122] Floyd RA, Schneider JE Jr, Dittmer DP. Methylene blue photoinactivation of RNA viruses. Antivir Res 2004;61(3):141–151. doi:10.1016/j.antiviral.2003.11.004.