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Antiviral optical techniques as a possible novel approach to COVID-19 treatment

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The current pandemic SARS-CoV-2 (also known as 2019-nCoV and COVID-19) viral infection is growing globally and has created a disastrous situation all over the world. One of the biggest challenges is that no drugs are available to treat this life-threatening disease. As no drugs are available for definitive treatment of this disease and the mortality rate is very high, there is an utmost need to cure the infection using novel technologies. This study will point out some new antimicrobial technologies that have great potentials for eradicating and preventing emerging infections. They can be considered as treatments of choice for viral infections in the future.

Keywords: SARS-CoV-2; COVID-19; light therapy; photodynamic therapy; photocatalysis; ARDS.

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1. Introduction

The emergence and spread of an acute respiratory disease threatens the modern world's health.[1] Today's world is facing a great challenge, a global pandemic that has had profound effects on public health and medical infrastructures globally, which was triggered by one of the most serious clusters of coronavirus disease-2019 (COVID-19). On February 11, 2020, the International Committee on Taxonomy of Viruses named the virus as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). The World Health Organization (WHO) named the disease caused by SARS-CoV-2 as COVID-19.[2]

Coronavirus is subdivided into four genera, including alpha, beta, gamma and delta (α, β, γ and δ), that are widespread in nature. Alpha and beta coronaviruses infect only mammals whereas gamma and delta coronaviruses mainly infect birds with a few infecting mammals.[3–5] Three of the mostly pathogenic strains of coronavirus are SARS-CoV, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS-CoV-2, which all belong to the genus beta coronavirus.[6,7] Some studies suggest that birds and bats are the natural reservoirs of the virus.[2,8]

The SARS-CoV-2 consists of a capsid with single-stranded positive-sense ribonucleic acid (ssRNA) that is integrated with a nucleoprotein in the matrix protein.[9] The SARS-CoV-2 spike (S) protein plays a critical role in viral infection and pathogenesis. It consists of S1 and S2 subunits. Similar to SARS-CoV, SARS-CoV-2 recognizes the angiotensin-converting enzyme 2 (ACE2) receptor via the receptor-binding domain (RBD) located in the S1 subunit.[10,11] The S2 subunit mediates fusion between the virus envelope and the host cell's membrane.[10,12,13]

Prothrombotic coagulopathy is often observed in critically ill COVID-19 patients with acute respiratory distress syndrome (ARDS). Similar to the 1918 pandemic, most of the patients losing their lives to COVID-19 today die from disease-related complications, such as pulmonary edema, pneumonia and ARDS.[14–16] ARDS is a common and important complication of this disease. ARDS is a critical lung condition that causes respiratory failure in critically ill patients and prevents enough oxygen from reaching the lungs and the bloodstream, which requires mechanical ventilation.[17]

The challenge posed by the coronavirus, which has led to global quarantines, indicates that the current human knowledge is incapable of responding to this emerging virus. Even before the WHO declared COVID-19 a pandemic, there was a deficiency of specific drugs for viral diseases. It is essential to provide timely treatment to achieve universal health coverage.[18] These problems suggest that new methods of treatment and prevention are needed in order to deal with such diseases. We begin this study with a brief description of the drugs currently used to treat COVID-19 and then discuss some new methods that can help to treat and prevent COVID-19.

2. Current Treatment Strategies for COVID-19

Unfortunately there is no reliable treatment for COVID-19 right now and international efforts are underway to address this need.[19] International (global) efforts are stepping up to find a definitive treatment for this disease. Supportive care, including oxygen therapy, fluid therapy and the use of broad-spectrum antibiotics to control secondary bacterial infections, is the most important management strategy.[20]

A list of potential drugs is provided in Table 1 and a number of commonly administered drugs are discussed in the following.

Remdesivir (development code GS-5734) is a broad-spectrum antiviral agent. Remdesivir is reported to be a promising antiviral drug against RNA viruses.[34] Holshue *et al.* reported that treatment of a COVID-19 patient with Remdesivir was associated with good results.[35] According to preliminary results of a major study by the National Institutes of Health, Remdesivir is a promising drug for the treatment and faster recovery of hospitalized patients diagnosed with COVID-19.[22] Nevertheless, Remdesivir is an investigational drug that has not been licensed or approved by any regulatory authority, and the safety and efficacy of Remdesivir for the treatment of COVID-19 have not been demonstrated yet.[36] Limited clinical data is also available regarding the emergency use of Remdesivir for the treatment of patients with COVID-19.[37] The manufacturer of the drug, Gilead Sciences, reported that more than half of 400 participants with severe COVID-19 recovered from their illness. However, it is difficult to interpret the results of this study without a placebo-controlled arm. On the

Table 1. A list of potential drugs/methods utilized to treat COVID-19.

Category	Drug/Method	Target
Nucleoside analogs	Remdesivir, Favipiravir, Ribavirin and Galidesivir	The RNA-dependent RNA polymerase and blocking viral RNA synthesis.[21–24]
Nonstructural proteins	Cinanserin, Flavonoids	The 3C-like protease inhibitors (3CLpro inhibitors).[25]
Nonstructural proteins	Diarylheptanoids	Papain-like protease inhibitors (PLP inhibitors).[26]
Receptor analog	Human recombinant soluble ACE2 (hrsACE2)	Blocks the binding of S-protein virus with ACE2.[27–29]
Antibody therapy	Convalescent plasma (CP) therapy	Collecting convalescent whole blood or plasma from patients who recovered from COVID-19 for transfusion to patients with early COVID-19.[30,31]
Antibody therapy	Monoclonal antibody (mAb)	CR3022, a SARS coronavirus-specific human monoclonal antibody, can bind potently with the receptor-binding domain of SARS-CoV-2.[32]
Antimalarial and immunomodulatory	Hydroxychloroquine and chloroquine	The mechanism of action of these drugs is against *Plasmodium* parasites. The mechanism of action of hydroxychloroquine/chloroquine against SARS-CoV-2 has yet to be fully elucidated.[33]

other hand, a smaller trial conducted in China showed that Remdesivir had no benefits compared to a placebo.[38] Moreover, Wang *et al.*[39] conducted a study on adult patients admitted to the hospital for severe COVID-19. In this study, Remdesivir administration was not associated with statistically significant clinical benefits. These studies had some limitations, include insufficient power to detect assumed differences in clinical outcomes, initiation of treatment quite late in the course of COVID-19 and the absence of data on infectious virus recovery or on possible emergence of reduced susceptibility to Remdesivir. Small clinical trials without a control group are commonly performed to find a treatment for COVID-19. It has also led to the rapid dissemination of conflicting information about Remdesivir, which has left people reeling.[40] These studies have some limitations including the small size of the cohort, insufficient power to detect assumed differences in the clinical outcomes, lack of a randomized control group, initiation of treatment quite late in the course of COVID-19 infection, type of supportive care (e.g., concomitant medications or variations in ventilatory practices) and the absence of data on infectious virus recovery or on possible emergence of reduced susceptibility to Remdesivir.[39,21] However, given the high mortality regardless of the use of Remdesivir, it is clear that treatment with an antiviral drug alone is unlikely to be sufficient.[41]

Hydroxychloroquine and chloroquine are widely used antimalarial drugs that have immunomodulatory activity.[42] At first, hydroxychloroquine and chloroquine gained unique considerations as potential therapeutic agents against SARS-CoV-2.[33,42] However, preliminary reports suggested that these drugs were associated with cardiac toxicity and increased frequency of ventricular arrhythmias in patients with COVID-19 infection, leading to decreased in-hospital survival.[43,44]

Interferons can prevent viral infections by inducing both innate and adaptive immune responses. Their beneficial effects in the early phases of infection are well expected.[28] Interferons possess a crucial role in the defense against coronavirus disease.[45] However, attention should be paid to the side-effects of these antiviral agents. Although these cytokines are released initially as a defense response, the window in which steroids might be beneficial to the patients with COVID-19 is very narrow. Elevated levels of plasma IL-6 and IL-8 are associated with the worsening of cytokine storm, which initially results in epithelial and endothelial cell death and vascular leakage and finally leads to inflammation exacerbation.[46]

The higher affinity of SARS-CoV-2 for binding to a genetically modified type of ACE2 known as human recombinant soluble ACE2 may represent a potential candidate for the treatment of COVID-19.[19,28]

3. Novel Treatment Strategies

Resistance to antiviral drugs is now well documented for several pathogenic viruses.[47,48] The novel coronavirus, which causes COVID-19, changes its genetic

code, which can lead to drug resistance. Viruses develop resistance to drugs that were once very effective. An example is azidothymidine (AZT), which was very promising for HIV treatment in the beginning. Resistance occurred due to mutations that ultimately enabled the virus to overcome the effect of AZT. Drug resistance is costly for the health service, for the patient who fails to gain maximum therapeutic benefit and for the community in which resistant viruses may spread.[49] Consequently, the development of antiviral drugs can become a great problem. Therefore, alternative therapies that can attack multiple targets in the virus may be a good solution to prevent resistance to viruses.[50]

Despite the use of various methods and drugs, the mortality rate of COVID-19 is still high. Common treatments should be used for several weeks to be effective against the microorganism, whereas application of light-based therapeutic techniques causes serious and irreversible damage of the microorganisms shortly after the initiation of light exposure.[49,51] Table 2 summarizes the advantages and limitations of light-based techniques that can be used to treat or prevent infectious diseases.

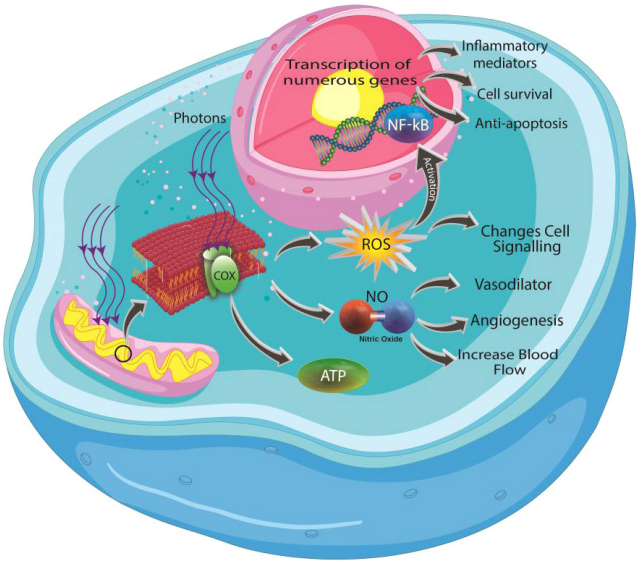
Table 2. Advantages and limitations of light-based techniques for the treatment and prevention of infectious diseases.

Optical technique	Method	Advantages	Limitations
Treatment	Antimicrobial photodynamic therapy (aPDT)	• Broad spectrum (lack of specificity for a microorganism).[54] • Development of resistance mechanisms is very low or even absent.[54,55] • Invasion of multiple targets in microorganisms.[49,56] • Immediate antimicrobial effect shortly after irradiation.[49] • Simple and controllable method.[49]	• Lack of quantitative assay to follow the viral photoinactivation process.[49] • A detailed photophysical and photochemical study is needed to investigate the interactions between the toxic species generated.[57]
	Photobiomodulation therapy (PBMT)	• Reduces the workload of the liver and kidneys (no need for metabolism of chemical drugs in the liver and kidneys).[19] • Expression of numerous genes involved in defense mechanisms.[58,59] • Vasodilation and angiogenesis (increases local blood flow).[60,61] • Decreases expression of pro-inflammatory factors.[62] • Increases the expression of anti-inflammatory cytokines.[62] • Increases innate cellular immunity.[63] • Broad spectrum (lack of specificity for a microorganism).[64,65]	• Lack of information about the effects of PBMT on local oxygen concentration (oxyhemoglobin, deoxyhemoglobin and total hemoglobin).[66] • Lack of extensive clinical studies at the molecular level. • Lack of suitable devices for further optimization.[67]
Prevention	Antimicrobial photocatalysis	• Simultaneous disinfection of diverse microorganisms.[68] • Low cost.[68,69] • Environment friendliness.[69] • Excellent chemical–physical stability.[70] • Broad spectrum (lack of specificity for a microorganism).[71] • Development of resistance mechanisms is very low or even absent.[72]	• Majority of studies focused on titanium dioxide (TiO_2).[73] • Not very efficient, especially due to their nonvisible light.[69]
	Spectroscopy techniques [Raman spectroscopy and Fourier-transform infrared (FT-IR) spectroscopy]	• Help with early and rapid diagnosis.[74] • Noninvasive and nondestructive.[74] • Biofluids analysis performed in seconds.[74] • High accuracy and stability.[75]	• Longer scanning time.[76] • Absorption of water, which overlaps with the amide I band of a protein.[77] • Need to compare spectroscopy techniques with other commonly used tools.[75]

Furthermore, SARS-CoV-2 can attack the liver and kidneys.[52,53] Therefore, the use of chemical drugs in oral and injection forms can increase the workload of these important organs. The next section discusses new treatments that can reduce the workload of the liver and kidneys.

3.1. *Light therapy*

Application of light to cause potential degradation and even perfect demineralization is a beneficial strategy for a green alternative. Photobiomodulation therapy, formerly known as low-level laser therapy (LLLT), includes application of light with the purpose of regulating the cellular function and immune system.[78–80] When light photons interact with the mitochondrial (the key initiating event in PBMT) cytochrome c oxidase (COX), which are specific biomolecules located in the mitochondria, they absorb the energy of the photons (Fig. 1).[81–83] Afterwards, the absorption of photonic energy by COX in the mitochondria serves as a generator of ROS (reactive oxygen species) and increases the activity of the entire electron transport chain, producing more adenosine triphosphate (ATP). Subsequently, NF-kB (nuclear factor kappa B), which plays a pivotal role in the cell signaling pathway, interacts with ROS in many ways.[84,85] NF-kB is transported into the nucleus and affects the expression of numerous genes (more than 150 genes). Many genes are involved in defense mechanisms against cell stress including inflammatory responses, early response (heat shock), anti-apoptosis, cellular migration and cell survival.[86,84]



Notes: LILI (low-intensity laser irradiation) penetrates tissue to variable depths depending on the wavelength, coherence, time and the tissue involved. A part of the photonic energy reaches the mitochondria and is absorbed by the COX. In addition, it increases enzyme activity and triphosphate (ATP) production and appears to initiate a burst of reactive oxygen species and nitric oxide (NO). Subsequently, the NF-kB will be activated. Downstream events include increased expression of numerous genes by NF-kB, which in turn increases the transcription of gene products including the ones involved in inflammation, early response (heat shock), anti-apoptosis, cellular migration and cell survival.

Fig. 1. Hypothesized schematic effect of the mechanisms of PBMT.

ROS act as a potent second messenger molecule at low concentrations.[84] Alteration of the intracellular levels of ROS can change the entire process of cell signaling. This interaction results in the production of transcription factors, enzyme activation, nucleic acid synthesis, culmination of the improved cellular mitochondrial energy metabolism and enhanced cell growth.[87–89] Although PBMT increases ROS generation, it increases antioxidants such as glutathione. Another mitochondrial protection mechanism for cell survival is an increase in Bcl2 (B-cell lymphoma 2).[80] The change in oxidation likely contributes to the release of NO during PBMT.[90] NO is generally considered as a vasodilator and angiogenic factor. Furthermore, it increases the local blood flow. However, in the context of COVID-19, it potentially attacks viruses, which is a much more important role.[91,92,88]

In addition to the improvement of mitochondrial metabolism (ATP synthesis),[81] studies have revealed that PBMT can reduce inflammation and edema. According to these studies, PBMT decreases the expression of pro-inflammatory factors such as IL-1β, IL-6, IL-10, COX-2 and IFN-γ and increases the expression of anti-inflammatory cytokines such as IL-2, IL-4 and IL-13.[80] In summary, all of these changes can control a cytokine storm in patients with ARDS symptoms. Subsequently, it will prevent tissue damage caused by the SARS-CoV-2 virus.

The membrane protein in the coronavirus envelope has a strong tendency to absorb light from ultraviolet (UV) to infrared (IR). This property could destabilize the virus and cause it to be particularly amenable to further actions of PBMT.[93,94] Evidence shows a direct link between vitamin D deficiency and COVID-19 mortality.[63,95] It has been reported that PBMT increases the production of ATP using red and near-infrared radiations and vitamin D using ultraviolet B (UVB) radiation.

Vitamin D and ATP have the primary role of activating the defense mechanisms of the immune system, which improves the resistance against SARS-CoV-2 and others infections agents.[63] Vitamin D increases innate cellular immunity, partially by inducing antimicrobial peptide gene expression, including human cathelicidin LL-37 and defensins.[63,96] Cathelicidins have antimicrobial activities against a wide spectrum of microorganisms.[97]

Treatment of lungs with this technique can open a new window to therapists, not only for the treatment of ARDS but also for the treatment of other diseases such as pneumonia and influenza. Liver and kidneys are weakened due to the metabolism of various drugs that the patient receives; therefore, PBMT can decrease their workload.[19,98] Efforts are needed to design and apply clinical trials of devices that are safe, noninvasive and easily employed for home use. Designing personal mobile devices that eradicate biological germs may be a simple form of mobile application in which the LED or laser is programmed to irradiate specific wavelengths.

3.2. *Photodynamic therapy*

Today, many researchers believe that there is an urgent need for investigating novel nonantibiotic strategies that can be used against infectious diseases.[55] One of these approaches is light-based antimicrobial therapy.[58] Photoactive compounds can potentially be used to prevent/eliminate microbial colonization in hospitals and healthcare centers.[99–101]

Photodynamic therapy (PDT) is a novel treatment for cancerous complications induced by viruses. Treating these cells with PDT can also reduce the viral load.[62,102,103] The procedure requires exposure of cells and tissues to a nontoxic photosensitizer (PS) followed by irradiation with a harmless visible light at an appropriate wavelength, usually in the red or near-infrared region, that is compatible with the absorption spectrum of the PS.[104]

Upon light activation, the PS reaches an excited singlet state (Fig. 2). Then, either the excited PS may decay back to the ground state by emitting fluorescence or the excited electron inverts to form a relatively long-lived triplet excited through intersystem crossing.[105] The triplet-excited PS can

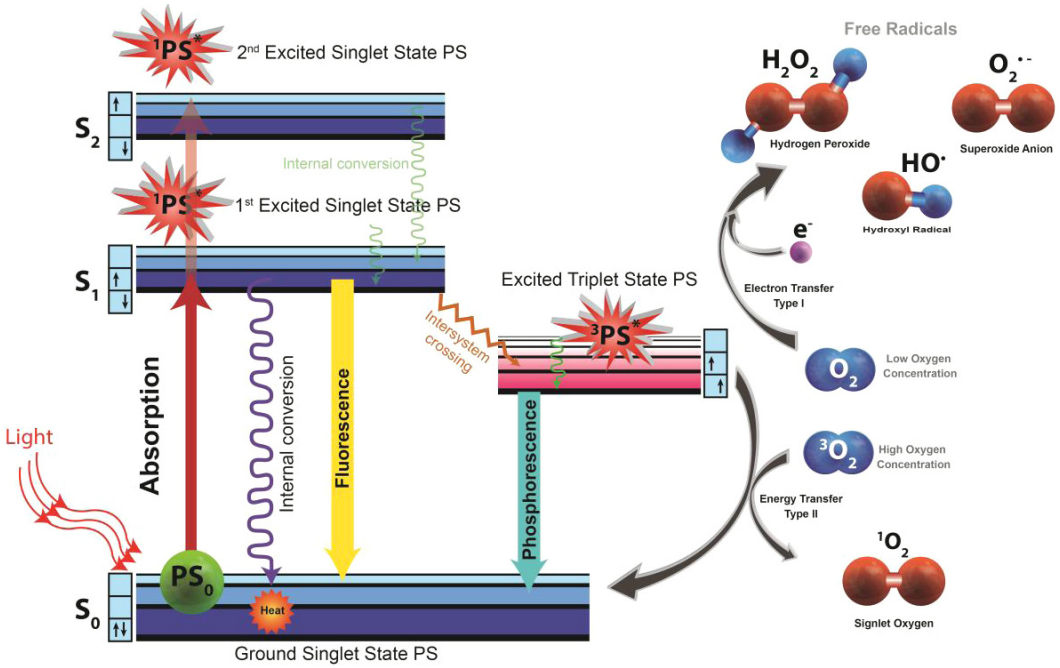


Fig. 2. Diagram representing a photochemical process during photodynamic therapy. Light (photon) with an appropriate energy is absorbed by a photosensitizer (PS_0) and it moves from a ground state (low-energy ground state) to an excited state. Photophysical processes can lead to luminescence through fluorescence or phosphorescence or heat generation through thermal relaxation. Alternately, the excited singlet-state PS ($^1PS^*$) may decay to a more stable triplet state through intersystem crossing. Among them, the excited triplet-state PS ($^3PS^*$) undergoes either a type-I or type-II photoreaction producing either reactive oxygen species or a singlet oxygen.

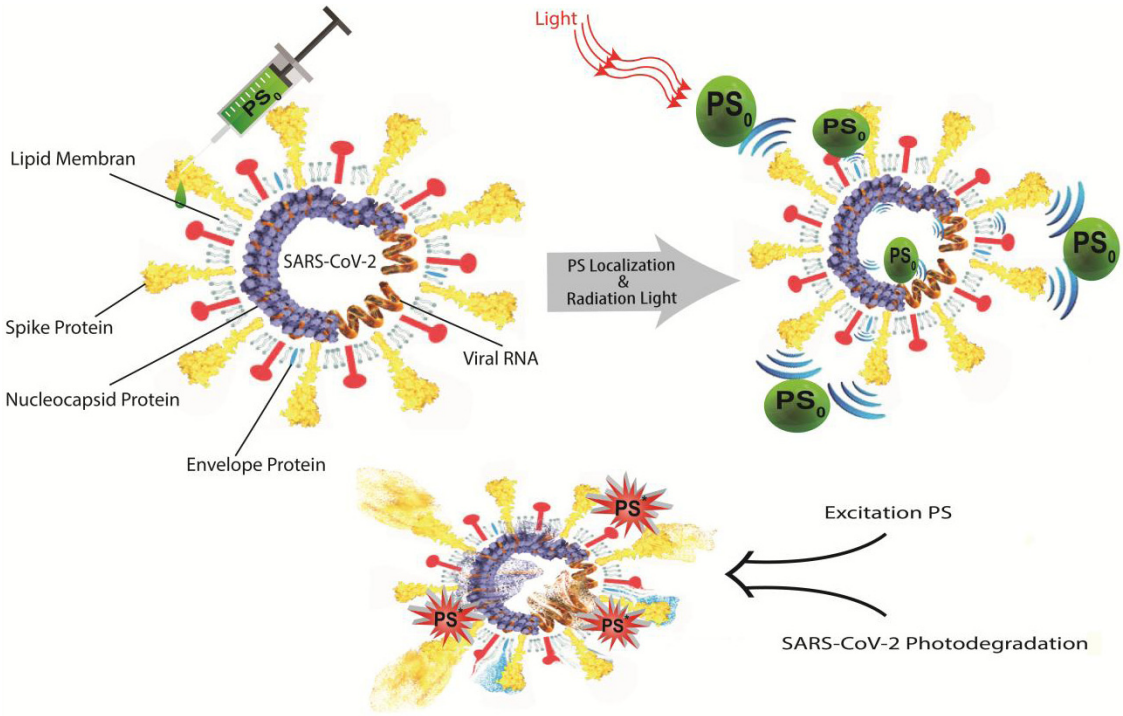


Fig. 3. Schematic of the effect of antimicrobial photodynamic therapy protocol on the specific targets in SARS-CoV-2.

undergo type-I (electron transfer) and/or type-II (energy transfer) reactions to produce highly reactive oxygen species.[106] During type-I photochemical mechanism, the triplet-excited PS reacts with biomolecules through a hydrogen atom (electron) transfer to form radicals, which react with molecular oxygen to generate radical and radical anion species such as superoxide anion radicals ($O_2^{\bullet -}$), hydroxyl radicals ($\bullet OH$), peroxide anion radicals ($O_2^{\bullet -2}$) and hydrogen peroxide (H_2O_2). Other oxidants that can form in subsequent steps include peroxyl radicals ($ROO\bullet$) and alkoxyl radicals ($RO\bullet$). Alternately, in type-II photochemical mechanism, the energy of the triplet-excited PS can be directly transferred to triplet oxygen ($^3O_2$) to produce singlet oxygen ($^1O_2$). The type-II pathway is highly dependent on the oxygen concentration.[59,107,108] It is worth noting that both competing mechanisms (type-I and type-II reactions) can occur simultaneously and the ratio between these processes is affected by the concentrations of $^3O_2$, nature and concentration of sensitizer and the reactivity of substrate or solvent.[60,109]

The PS diversity provides different properties and should be tested for the purpose of SARS-CoV-2.[110] The positive charge on the PS molecule promotes a tight electrostatic interaction with the negative charge in the nucleic acid or outer structures of the virus (capsids and envelopes) (see Fig. 3). It has been shown that enveloped viruses are significantly more sensitive to damages caused by photodynamic therapy compared to nonenveloped viruses.[49] Unsaturated lipids in the envelope of SARS-CoV-2 and the major envelope proteins of this virus [such as spike (S1 and S2) proteins] are important PDT targets that cause photodamage to these PS binding sites, resulting in the modification of their structure and avoiding cell infection and virus replication (Fig. 3).[49,111] Following the activation of PS localized in nucleic acid or outer structures of SARS-CoV-2 by light, sugar sections are usually photo-oxidated by radicals (generated via type-I process) and guanine residues are attacked by singlet oxygen (generated via type-II process).[49]

As a novel way to control viral, bacterial and fungal infections, PS-based nanomaterials have been studied in photodynamic therapy techniques, which allow access to areas with complex anatomy. If the nanomaterials bond to monoclonal antibodies, which can target the lung tissue specifically, less damage occurs in the adjacent tissues.[54] In addition, PS can be directly delivered to the respiratory system via nebulization. The side-effects of intravenous

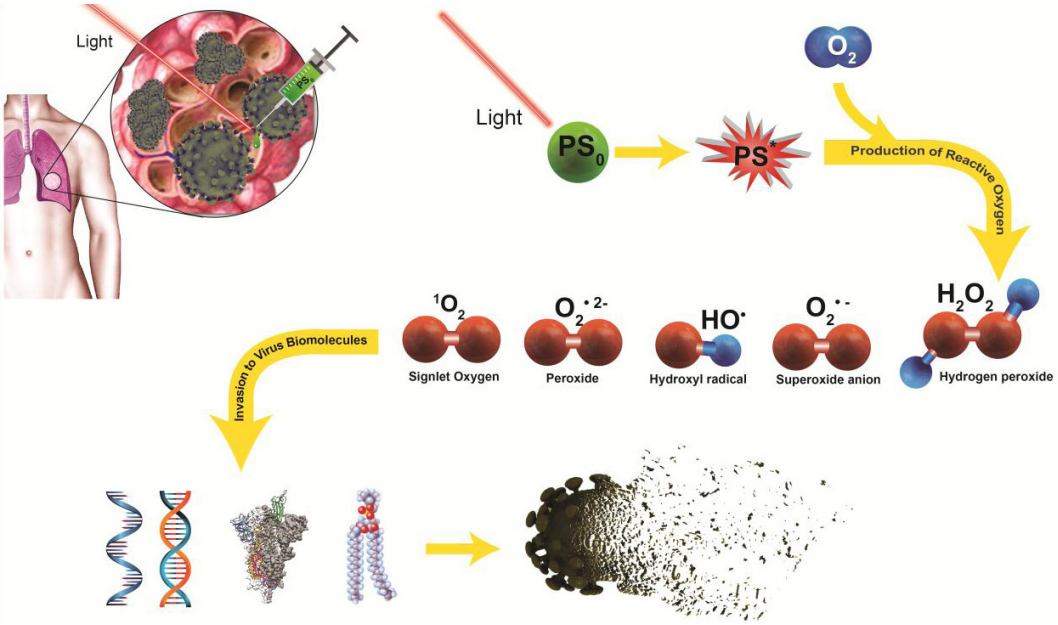


Fig. 4. Schematic illustration of aPDT and the main therapeutic effects. aPDT is initiated with transporting photosensitizer (PS_0) to the target tissue. PS_0 moves to the target tissue site through the bloodstream and is uptaken by the target cells. Once PS_0 is localized in the target cells, the site is irradiated. Photons from the light are absorbed by PS_0, which results in energy transfer to PS^*. Exposure to the light absorbed by PS induces several therapeutic effects. DNA, RNA, lipids, proteins and polysaccharides can all be damaged by aPDT-generated ROS, resulting in virus elimination.

injection and photodynamic inactivation can be decreased and drug delivery problems can be overcome in the method.[50]

In a biological condition, the reactive species generated by the photodynamic method can react directly with a considerable number of biomolecules (Fig. 4), mostly amino acids such as Trp, His and Met, nucleic acids (exclusively guanine) and unsaturated lipids.[105,112–114]

The first photodynamic inactivation protocol to combat viruses was reported in 1928 followed by clinical treatment of herpes infection in the United States in the 1970s.[50] In recent years, this technique is increasingly employed to treat thoracic malignancies.[115] Indeed, PDT has been approved for the treatment of lung cancer with excellent results.[54] Additionally, it has shown promising results in extracorporeal applications, e.g., disinfection of blood products (viruses transmitted through blood products and transfusions). To date, many *in-vitro*, animal and clinical trial studies have used PDT for treating respiratory tract infections, which can be considered a good starting point.[50] The pharyngotonsillitis PDT can help to reduce the number of microorganisms in the oropharynx.[116] In a study using clinical PDT protocol against pharyngotonsillitis, the authors reported a reduction of more than 90% in the symptoms related to the disease.[117] In 2017, Lago and Furtado demonstrated that a combination of PDT and PBMT was effective against herpes simplex in the nose wing region.[118]

A general critical issue in the therapeutic use of PDT is the efficient transfer of light. The exterior surfaces of the body (e.g., the skin or mucosa) are easily accessible by extracorporeal illumination, thus PDT has been highly successful for the treatment of cancers and infectious and inflammatory diseases in these regions. However, the condition is more intricate for interior organs such as the lung because of the limited capacity of tissues to be infiltrated by light.[119] For this purpose, if we could deliver the PS to the internal organs (e.g., the lung or liver), we may be able to irradiate them with laser light.[19] As SARS-CoV-2 mainly affects the lungs, it is relatively easy to irradiate these internal organs endoscopically using an optical fiber, which can be introduced through the nose. In fact, aPDT has been already used to inactivate the bacteria in the nostrils.[54,120]

In 2017, Geralde *et al.*[119] reported important advances in using extracorporeal irradiation. They found that the infrared light could pass through the

mouse chest although its intensity decreased. They performed a series of light penetration experiments at 780 nm in post-mortem mice, which showed that about 50% of the light was absorbed and scattered in the lung. This activity is an important achievement in clinical application, which will clearly be useful for treatment purposes. Extracorporeal illumination can be utilized as a single therapy or as an antibiotic adjuvant against SARS-CoV-2.[116]

Since viruses are changing continuously and genetic changes through mutation occur continuously in them,[121] the emergence of more invasive and more lethal viruses in the future is a possibility. Therefore, it is significant to find treatment methods that are not affected by the mutations and extensively attack several targets in the pathogen. PDT attacks different therapeutic targets in viruses[122]; therefore, it is highly unlikely that the mutations occurring in the virus can limit the PDT antimicrobial properties. Due to these features, there is a high probability that PDT will be effective for the treatment of COVID-19 as well as the prevention of COVID-19 pandemic and post-infectious complications.

In addition to medical disciplines, this technique is closely related to physics and chemistry.[61] Therefore, it is important that the technique is developed in a multidisciplinary manner. A close collaboration is needed between medical doctors of different specialties, physicists and biochemists. If pursued successfully, PDT might become a blessing for patients with COVID-19.

4. Novel Preventive Strategies

Aerosols are a suspension of particles formed by solid particles or liquid droplets dispersed and suspended in the air. When a person infected with the virus coughs, sneezes, breathes vigorously or speaks loudly, the SARS-CoV-2 could be spread via the exhaled air and dissolve in the aerosol to form a bioaerosol.[123]

The term "bioaerosol" refers to airborne particles originating from biological sources. In such cases, a bioaerosol can refer to aerosolized cells (e.g., *Legionella pneumophila* in an air vent), viruses (e.g., a cough containing MERS or SARS viruses), spores (e.g., Anthrax spores during industrial processing of contaminated materials such as wool) or biological cell remnants (e.g., endotoxin or peptidoglycan).[124]

4.1. *Air purification*

Concerns about pandemics of airborne viruses, such as influenza virus H1N1 and severe acute respiratory syndrome (SARS-CoV, SARS-CoV-2), have attracted global attention to the development of air purification methods for disinfecting airborne microorganisms.[125] If the transmission is interrupted, the prevalence of COVID-19 may eventually decrease.

Bioaerosols attached to other particles, also known as biological rafts, often enhance the survival of cells or viruses.[124] The results of the very recent studies suggest that SARS-CoV-2 may aerosolize, since the virus can remain viable and infectious in the bioaerosol for several hours and on the surfaces for up to days (depending on the inoculum shed).[123,126,127]

Based on a study by the US Environmental Protection Agency (EPA), indoor air pollution poses a considerably higher risk compared to outdoor air pollution.[128] Since most of the healthcare workers spend a substantial amount of time in the hospitals, indoor air contamination poses a critical threat to them.[129] Furthermore, the WHO states that every individual has a right to breathe healthy indoor air.[130] The WHO also argues that ensuring acceptable indoor air quality is the responsibility of all people.

Traditional filtration systems include the use of activated carbon filters, HEPA air purifier filter, ozonation, air ionization and Bio-Guard filters (in which airborne biological particles that contain living organisms or particles released from living organisms are collected on the surface of a filter), which are all good systems for overcoming indoor air pollution. Nonetheless, these antimicrobial compounds that coat filters are generally effective over a short period of time. Due to the accumulation of nonbiological dust, traditional filtration systems require a large pressure drop, and they need to be replaced regularly to inhibit the possible return of biological airborne contaminants into the indoor environment. In other words, none of these systems are completely effective.[131,132]

Photocatalysts have been widely used worldwide as potential antimicrobial agents to overcome several environmental challenges in the modern society.[133,134] Photocatalysis is an innovative and promising technology. This technique emerged as an effective green solution for antimicrobial

disinfection applications.[135] Interest in the application of the photocatalytic properties of TiO_2 was revived when Fujishima and Honda reported photoelectrolysis of water,[73] which led to studies in the destruction of liquid organic compounds by a semiconducting photocatalyst.[136] In addition, Matsunaga *et al.*[137] used photocatalysis for the disinfection of pathogens for the first time.

Photocatalytic reactor systems can be classified according to their configuration. The major types used in air purification units include plate, annular, honeycomb monolith and fluidized-bed reactors.[138]

Antimicrobial photocatalysis is described as a process in which semiconductor (SC) nanoparticles are irradiated with light to generate ROS to kill various types of microorganisms.[137] The light source that is most commonly used in this technique is artificial UV light at a wavelength range of 254–365 nm.[68,139,140] In the process of photocatalysis (Fig. 5), a photocatalytic material (semiconductor) is irradiated at a compatible wavelength (energy equal to or greater than the bandgap of semiconductor).[135,141] Afterwards, the electrons (e^-) elevate from the valence band (VB) and are absorbed onto the conduction band (CB), which generates a positive electron–hole pair on the valence band (h^+ VB). Thereafter, excited e^- in the CB and the positive electron–hole pair generated in the VB immigrate toward the surface of the semiconductor. At the same time, oxidation and reduction reactions are complete at the surface of the semiconductor. In the CB, the electrons react with oxygen (O_2) which gives rise to the generation of superoxide radicals ($\bullet O_2^-$) and hydroperoxide radicals ($\bullet HO_2$). In general, the photocatalytic material photodegrades the pollutants (virus proteins, genome and envelope) by the ROSs in the indoor air.[68,135,142]

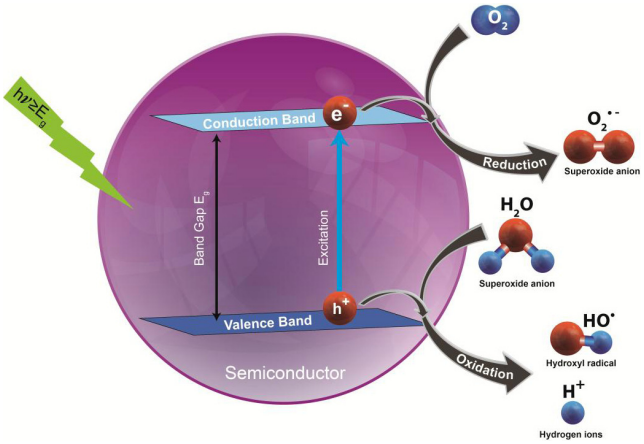


Fig. 5. The fundamental mechanism of photocatalysis on a semiconductor particle surface. Semiconductor excitation occurs by bandgap illumination, leading to the creation of electrons (e^-) in the conduction band and holes (h^+) in the valance band ($h\nu \geq E_g$: energy equal to or greater than the bandgap of semiconductor).

Antimicrobial photocatalysis can be widely used for air (Fig. 6), water and surface disinfection.[143,144] It has several advantages, including the simultaneous disinfection of diverse microorganisms, relatively low cost and ease of operation and maintenance.[68] Following the attack of SARS virus in 2003, Howells studied a system, based on photocatalytic disinfection, to control the spread of infectious microorganisms such as SARS virus.[129] Kim and Jang investigated the photocatalysis reactions for simultaneous inactivation of airborne MS2 viruses and degradation of the generated ozone toward a flow-through air disinfection system with high flow rates. They found that this system had the potential to serve as an alternative to conventional UV-based air purifiers.[68] Ren *et al.* provided an overview of 27 studies summarizing photocatalysts used for the photodisinfection of different pathogens in the air. Twenty-five studies reported that the extent of photodisinfection of the pathogens was $\geq 90\%$, while two studies showed the extents of $\sim 50\%$ and $\sim 70\%$.[73] In 2020, Martínez-Montelongo *et al.*[145] evaluated the photocatalytic antibacterial activity of air filters for the disinfection of indoor air (dentistry clinics). In this study, bacterial growth inhibitions up to 99% were achieved for both Gram-negative and Gram-positive bacteria. A study of the photocatalytic antibacterial behavior of air filters fabricated from zinc-imidazolate metal–organic frameworks (MOFs) (ZIF-8) showed marked performance for integrated pollution control with $> 99.99\%$ photocatalytic killing efficiency against airborne bacteria in 30 min.[146] In another study, Nakano *et al.*[147] demonstrated the inactivation of influenza virus through TiO_2 photocatalysis using TiO_2 nanoparticles immobilized on a glass plate. The results of their study revealed that the viral titers dramatically reduced by the photocatalytic reaction such that a viral reduction of approximately 4-$\log_{10}$ was observed within a short irradiation time. Liu *et al.*[148] investigated the antiviral activity of a nanocomposite under dark conditions. They reported that Cu(II)–TiO_2 completely inactivated the bacteriophage within 30 min of visible light irradiation. In 2007, Hajkova *et al.*[149]

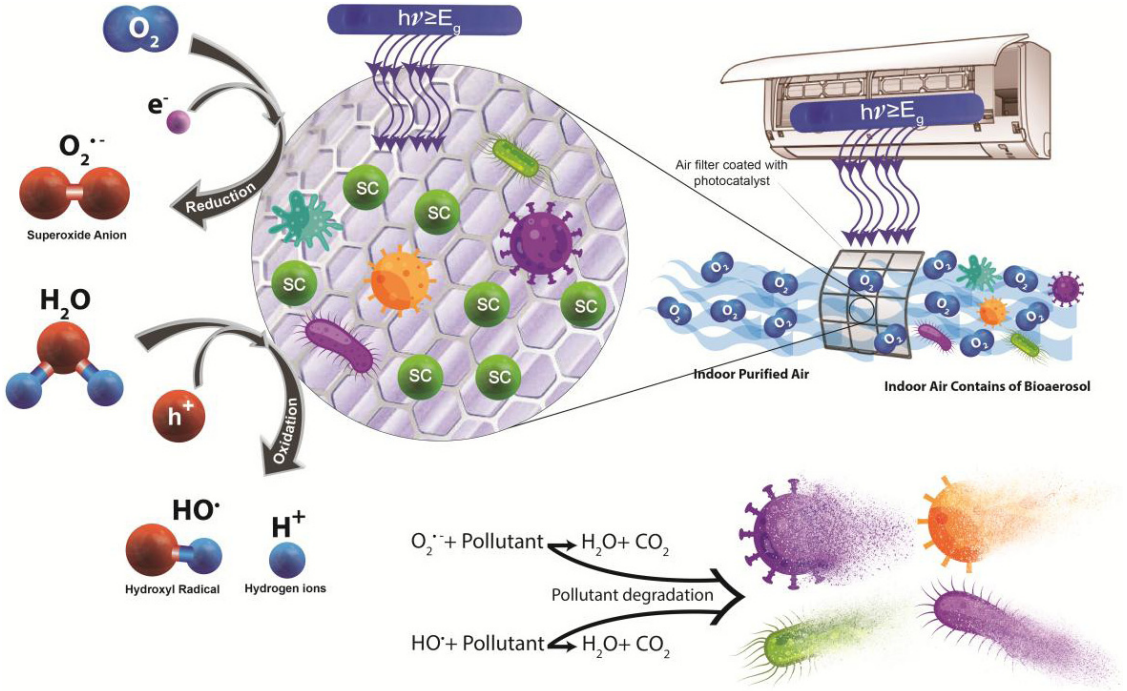


Fig. 6. Schematic for the representation of photocatalytic-based filter for the air purification process. Air enters the purifier machine; then, it enters the photocatalytic cleaning section (the filters are coated with a photocatalyst material). Subsequently, the photocatalytic material (SC) is irradiated at a compatible wavelength (energy equal to or greater than the bandgap of semiconductor: $h\nu \geq E_g$) to produce ROSs. Eventually, it breaks down organic compounds and thus reduces fungal, bacterial and viral microorganisms adsorbed on the catalyst's surface.

described the antibacterial and antiviral effects of TiO_2 thin films. In this study, a 100% antiviral effect was achieved after 6 h of illumination. In 2008, Gerrity *et al.*[150] evaluated the efficacy of TiO_2 photocatalytic disinfection in four bacteriophages. The authors observed that 1 mg/L of Degussa P25 TiO_2 irradiated by low-pressure UV light reduced the dose requirements for viral inactivation in comparison to UV light alone. We also studied a combination of antimicrobial photocatalysis and aPDT to eradicate the extensively drug-resistant colistin-resistant *Acinetobacter baumannii* (XDR–CO-Ab).[133] The results showed that simultaneous use of aPDT and antimicrobial photocatalysis methods had amazing effects such that 99.32% of extensively drug-resistant colistin-resistant *Acinetobacter baumannii* were killed.

Evidence suggests that SARS-CoV-2 is transmitted through direct contact and bioaerosols.[151] People who are in contact with or care for patients are at a higher risk of acquiring COVID-19. Inevitably, this places medical staff at a high risk of infection. In order to eliminate this pandemic, protecting healthcare workers is of paramount importance. Therefore, using a photocatalytic technique can play an important role in cleaning the indoor air in rooms or places where the patients with COVID-19 are hospitalized.

5. Conclusion

COVID-19 is a major threat to global public health. Scientists in all areas should manage the main dramatic anarchy of the century as soon as possible. The specific mechanism of the virus remains unknown, and there is no known effective antiviral agent to control the COVID-19 outbreak and inactivate SARS-CoV-2 virus.[9] It is important to control the source of infection, block the route of transmission and use the existing drugs and means to control the progress of the disease proactively.

Lessons learned from this major epidemic can be applied to the new pandemic. We should synchronize our speed with the progression of this disease. In other words, we should strive to develop specific drugs, promote research activities, develop new methods and reduce morbidity and mortality of COVID-19 in order to enhance the safety of the

population.[28] There is a rapidly growing need for novel techniques for viral infection control. PBMT and PDT are well-established therapeutic techniques that have attracted the attention of many scientists.[119] The PBMT process focuses on tissue oxygenation, alteration of the cell signaling cascades and reduction of cytokine storm caused by severe inflammation.[80,88,152] PDT performance can be improved by using nanoparticles, designing new photosensitizers in the nanoscale and stimulating them on the target tissues to obtain the best effects.[99,133] These methods may be used as an adjuvant therapy or even an alternative therapy without side-effects and drug interactions. The combination of these methods can improve the function of the cells and the immune system.

Photocatalysis is an effective advanced oxidation process (AOP) technology that offers several environmental and practical advantages over the conventional biological or physical disinfection processes. It represents one of the most promising options for degrading and mineralizing bioaerosols regardless of the weather.[68,153] Instead of simply trapping pollutants (which still have to be disposed), photocatalytic technology completely transforms the harmful bioaerosols and effectively oxidizes the organic compounds.[154] It can improve the medical staffs' respiratory health and the overall air quality in hospitals.

To sum up, this disease is perhaps a flick or inspiration. Human knowledge should be vigorously challenged to create a revolution. It warns the human beings to be prepared to face difficult challenges in the future to address the concerns associated with impending crises. Everyone in the world should work with governments, health workers and other front-line responders to provide protection from sickness so that the ship of life on this beautiful planet continues its tranquil journey to its destined horizon.

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Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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