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Invited Review

Light-based technologies for management of COVID-19 pandemic crisis

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ABSTRACT

The global dissemination of the novel coronavirus disease (COVID-19) has accelerated the need for the implementation of effective antimicrobial strategies to target the causative agent SARS-CoV-2. Light-based technologies have a demonstrable broad range of activity over standard chemotherapeutic antimicrobials and conventional disinfectants, negligible emergence of resistance, and the capability to modulate the host immune response. This perspective article identifies the benefits, challenges, and pitfalls of repurposing light-based strategies to combat the emergence of COVID-19 pandemic.

1. Introduction

The pandemic spread of the novel coronavirus disease (COVID-19), caused by the SARS-CoV-2 virus, is a red-alert global health threat [1,2]. In December 2019, COVID-19 expanded from Wuhan throughout China and was then exported throughout the world [1–4]. So far, more than 10 million people have been diagnosed with COVID-19 infection, and many more are expected to be diagnosed within the coming months [5,6]. As the epidemic evolves, national and global organizations are facing an urgent need to coordinate and combat this unprecedented large-scale public health crisis [6].

The epidemiological features of COVID-19 (*i.e.*, severity, full spectrum of disease, transmissibility) have not been fully dissected [7]. The consensus is that the risk for severe acute disease symptoms and death is higher among the elderly and the immunocompromised [8–10]. In severe cases, infected patients need to be transferred to intensive care units for tracheal intubation [11]. This phenomenon is particularly worrisome because it can overwhelm healthcare facilities during the epidemic peak [10–13].

The spread and persistence of SARS-CoV-2 in diverse environments, such as healthcare, community, and residential areas, underlines the urgency for developing effective decontamination approaches as the pandemic crisis evolves [14]. A successful disinfection strategy coupled with additional infection-prevention countermeasures may substantially reduce transmissibility from asymptomatic carriers, a feature that is considered pivotal in the rapid dissemination of SARS-CoV-2. New light-mediated disinfection protocols are currently validated in hospitals and healthcare facilities for surface, air, and water as well as

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personal protective equipment (PPE), including eyewear, N95 respirators, and masks. Additionally, photobiomodulation, a light-based anti-inflammatory therapy, may have some palliative effects on patients suffering from severe COVID-19. This review examines the potential of light-based technologies to prevent COVID-19 infection and control its dissemination by direct viral inactivation and to treat COVID-19 by modulating the host immune system. The direct antimicrobial actions of solar and UV radiation, photodynamic therapy, antimicrobial blue light, and ultrafast pulsed lasers for disinfection or *in vivo* use are considered, and the application of photobiomodulation to stimulate the host to mount an anti-viral response is discussed.

2. SARS-CoV-2 Stability Outside The Human Body

SARS-CoV-2 is highly infectious [15] and transmission occurs through contaminated air, water, and surfaces, which plays a pivotal role in its unbridled dissemination. A recent study by van Doremalen and colleagues investigated the stability of SARS-CoV-2 in aerosols and on inanimate surfaces (*e.g.*, glass, metal, plastic, or cardboard) that can act as important transmission vectors [16]. Their findings suggest that aerosol and fomite transmission of SARS-CoV-2 is likely, indicating that the virus can remain viable and infectious for hours in aerosols and up to days on surfaces. This is in agreement with a recent comparative analysis of 22 studies looking at the persistence of a broader panel of human coronaviruses on inanimate surfaces [17] This study included prominent pathogenic coronavirus species such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and endemic human coronaviruses (HCoV) and concluded that: 1) viruses can remain infectious from 2 h to 9 days; 2) incubation temperature is critical, as some viruses can remain viable at 4 °C for up to 28 days whereas at 30–40 °C viral viability is reduced.

3. Historical Milestones of Antimicrobial Light

The microbicidal effects of light have been widely known for more than a century. In 1885, Duclaux experimented with several microbial species and concluded that "sunlight is the best, cheapest, and most universally applicable microbicidal agent that we have" [18]. As early as 1877, Downes and Blunt observed that light could effectively kill a series of microorganisms and reported that this effect was dependent on light parameters such as intensity, duration (*i.e.,* light dose) and that the shortest wavelengths (*e.g.,* blue to ultraviolet light) were the most effective [19] The first report on the virucidal effects of UV radiation dates back to 1928 when Rivers and Gates used UV light to inactivate viral particles in suspension and proved the efficacy of the method through subsequent subcutaneous inoculation of rabbits [20].

In 1903, Niels Finsen was awarded the Nobel Prize in Physiology or Medicine for his contribution to the treatment of infectious diseases, especially cutaneous tuberculosis, using visible light [21,22]. Virtually at the same time, Herman Von Tappeiner and Oscar Raab discovered by accident that the use of fluorescent dyes could enhance the microbial killing effect of visible light via photodynamic reactions [22]. By the 1930s, germicidal low-pressure Mercury (Hg) discharge lamps emitting quasi-monochromatic UV-C light (peak emission at 254 nm) had been introduced into the market as highly efficient disinfection equipment [23]. Thus, since the pre-antibiotic era, light-based strategies have been extensively studied and used to treat and prevent infections [24]. However, each photoinactivation strategy has its pros and cons that must be carefully considered when designing a new microbial control strategy.

4. Natural Ultraviolet Light

Ultraviolet (UV) radiation is naturally and ubiquitously emitted by the sun, representing 10% of its total light output. Only a small portion of the sunlight spectra has direct antimicrobial properties (UV-C). However, since most UV-C light is filtered by the atmospheric ozone layer, in practical terms, the antimicrobial activity associated with sunlight is mostly caused by photochemical reactions induced by UV-A and UV-B photons which are absorbed by endogenous chromophores such as amino acid residues, flavins, and porphyrin derivatives [25]. While UV-A alone does not seem to exert any significant virucidal effects, natural and artificial sunlight, as well as radiation in the UV-B spectrum, have been shown to inactivate bacteriophages and human viruses [26]. A model for the potential of solar UV radiation to inactivate viruses aerosolized in the atmosphere concluded that a full day of sun exposure would on average decrease the infectivity of UV-sensitive viruses by 3 $\log_{10}$ [27].

Besides its virucidal potential, solar UV radiation can also play a protective role against infectious diseases via its modulating effect on vitamin D production [28]. Vitamin D is known to upregulate the production of human cathelicidin, LL-37. This antimicrobial peptide has both antimicrobial and antiendotoxin activities, and also attenuates the production of proinflammatory cytokines which typically accompany respiratory tract infections. Accordingly, it was recently suggested that vitamin D could reduce the incidence, severity, and risk of death due to respiratory tract infections, notably those caused by COVID-19 [29]. However, conclusive evidence for an association between vitamin D supplementation and decreased risk of respiratory tract infections is still lacking.

UV-C is directly absorbed by pyrimidine bases causing their dimerization, which leads to viral inactivation via DNA or RNA damage [30]. Thymine is the main chromophore in DNA while uracil is its counterpart in RNA. Upon UV-C exposure, thymine and uracil form cyclobutane-dimers and pyrimidine-protein cross-links [30]. It must be stressed that UV-C usage must be limited to inanimate objects since it is highly dangerous to human skin. The viral protein coat has been shown to protect nucleic acids from UV-C radiation, by shielding the RNA, quenching the excited states of RNA, and/or by surrounding the bases with a hydrophobic environment and limiting the mobility of the individual bases. This results in a reduction of the overall rate of photoreactions, which allows the formation of non-cyclobutane-type dipyrimidines and uridine hydrates. Viral coating proteins themselves may suffer UV photodamage and become cross-linked to RNA.

The International Ultraviolet Association (IUVA) recently released a fact sheet detailing the efficacy of UV on SARS-CoV-2 [31] in which they reviewed all the appropriate requirements for the safety of UV-C disinfection devices and discussed the corresponding performance standards and validation protocols. Coronaviruses display a wide range of UV-C LD_{90} (UV-C dose necessary to inactivate 90% of a microbial population) values, from 7 to 241 J/m^2 so one might assume that the UV-C susceptibility of the novel SARS-CoV-2 (COVID-19) virus probably lies within this range [32]. Therefore, based on previous studies with SARS-CoV-1 and other RNA-based coronaviruses, UV-C light can be used to effectively inactivate such pathogens present in the air, liquids and over several surfaces [33,34].

5. Ultraviolet Germicidal Irradiation (UVGI)

UV-C lamps have long been used in hospital and industrial settings for decontamination purposes. In the context of a mitigation approach to infection spreading, UV-C can be particularly helpful in the inactivation of virus-containing aerosols and surfaces.

Air disinfection via upper-room germicidal UV-C light fixtures may be able to reduce viral transmission via the airborne route. Accordingly, an observational study during the 1957 influenza pandemic reported that patients housed in hospital wards with upper-room UV-C had an infection rate of 1.9%, compared to an infection rate of 18.9% among patients housed in wards without UV-C [35]. However, it is important to note that the germicidal effect of UV-C seems to be strongly dependent on the relative humidity of the air, with UV-C effectiveness against influenza virus decreasing with increasing relative humidity [36].

The potential of viral spreading via contaminated surfaces depends on the ability of the virus to maintain infectivity in the environment, which in turn is influenced by several biological, physical, and chemical factors, including the type of virus, temperature, relative humidity, and type of surface [37]. Importantly, single-stranded nucleic acid (ssRNA and ssDNA) viruses were more susceptible to UV inactivation than viruses with double-stranded nucleic acid (dsRNA and dsDNA). Also, the UV dose necessary to achieve the same level of virus inactivation at 85% relative humidity (RH) was higher than that at 55% RH [37].

In a recent study, Fischer et al. showed that UV-C light can inactivate more than 99.9% of SARS-CoV-2 viral particles deposited over the filtering material of N95 masks and stainless steel surface [38]. As expected, inactivation kinetics over stainless steel was much faster (i.e., more than 99.9% for (0.33 J/cm^2). However, after sufficient exposure (1.98 J/cm^2) UV-C could promote germicidal efficacy levels that were similar to those promoted by ethanol, dry heat or vaporized hydrogen peroxide. Older studies have hypothesized that the necessary dose to inactivate 90% of viruses present in N95 filtering facepiece respirator (FFR) material would be about 30 times higher than over the surface of non-porous materials [39]. This was an interesting estimation, but we should keep in mind that UV-C emission spectrum and irradiance of different UV-C equipment as well as material composition are widely variable [40]. Therefore, such estimatives cannot be used as a robust procedure and experimental demonstrations must always be presented. Indeed, a recent *in silico* study demonstrated that for effective and fast decontamination one should consider the FFR shape besides the optical properties of the FFR model, which has to be determined at the UV-C specific wavelength [41]. Even though UV does not seem to affect the filtrating capacity of FFRs, it is important to note that high UV-C doses can lead to reduced tensile strength of its materials [42,43].

The combination of multiple light wavelengths has been explored for cosmetic, environmental (water disinfection) and clinical (microbial catheter disinfection) applications. However, the precise photobiological mechanism of action and the experimental workflow to develop a marketable application is still missing [44,45].

It must be remarked that UV-C light at 254 nm is harmful to the eyes and skin and, therefore, it is recommended to use it in setups that avoid direct human exposure. Although, far-UV-C (207–222 nm) has been proposed as a disinfection technology that seems to be safer to human exposure [46]. This has been claimed because far-UV-C range is strongly absorbed by amino acid residues and, therefore, is further blocked by the acellular stratum corneum of the skin and the cornea of the eye, leading to lower levels of UV-C light reaching the cellular layers of eyes and skin. However, as far as our knowledge goes, robust studies showing the actual safety of far-UV-C towards animal tissues in short and long terms have not been strongly established and degradation of proteins can also lead to serious eye and skin damages. Thus, we can only recommend UV-C application to inanimate objects. Additionally, far-UV-C technology is not broadly available in the market yet and the cost is far higher than common LP-Hg lamps. On the other hand, UV-C LED technology is limited to very compact applications. The shortest wavelengths available are around 255 nm, with the price per Watt being up to 1000 times higher than that of LP-Hg lamps, while displaying an energy efficiency (< 1%) far lower than that of LP-Hg lamps (25–40%) at 254 nm.

6. Photoantimicrobials and Photodynamic Therapy

Visible light can exert antiviral effects via photodynamic mechanisms that are initiated upon absorption of light by exogenous photosensitizer compounds, such as phenothiazinium salts, porphyrins, nanoparticles, and others [47–50]. The inactivation of microorganisms and viruses by visible light is based on the generation of lethal oxidant species via photosensitized oxidation reactions, which usually require three components: the chromophore, termed the photosensitizer (PS), light, and oxygen, even though some PS may also work through alternative reactions in the absence of oxygen [51]. After light absorption, excited oxygen states are quickly formed, initially in the singlet, and subsequently in the triplet states (*i.e.*, considering the photocycle of organic molecules). These species can release the excitation energy in the form of light emission (*e.g.*, fluorescence and phosphorescence) or heat release (non-radiative decay). Since excited states are intrinsically more reactive than ground states, energy and electron transfer reactions can occur. There are two main mechanisms of photosensitized oxidation: Type I reactions depend on the encounter of the excited species with biological substrates. These reactions usually occur through electron or hydrogen abstraction, leading to radical chain reactions; Type II reactions rely on energy transfer reaction from the PS triplet state to molecular oxygen, generating singlet oxygen ($^1O_2$) (Fig. 1) [52]. Spacially, type I reactions require the PS to be within a subnanometer distance to the virus, whereas type II reactions allow singlet oxygen diffusion to more than 100 nm [51].

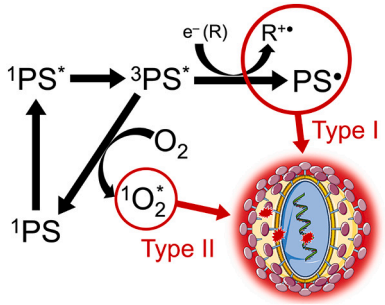

Fig. 1. Mechanisms of photosensitized oxidation reactions. The photosensitizer (PS) is a molecule capable of absorbing light depending on its specific absorption spectra. Once excited, the PS is converted from the ground state ^{1}PS to its singlet excited ^{1}PS* and triplet excited ^{3}PS* states. Via Type I (contact-dependent) reactions both ^{1}PS* and ^{3}PS* can react directly with O_2 or biomolecules, like carbohydrates, lipids, proteins, or nucleic acids, resulting in the formation of radicals capable of initiating redox chain reactions. Otherwise, ^{3}PS* can react with molecular oxygen ($^3O_2$), via the Type II (energy transfer) reaction, generating the reactive state of singlet oxygen ($^1O_2$).

Light energy is thus converted into oxidation potential that can damage biomolecules. Antimicrobial photodynamic therapy (aPDT) is based on this process and it has been used to treat localized microbial infections caused by viruses, bacteria, fungi, and parasites [53]. Among the many pathogens that can be targeted by aPDT, viruses are perhaps the most vulnerable, as they depend on entering a host cell for survival and replication and can be inactivated by damaging the capsid or envelope molecules (lipids, carbohydrates, proteins) or internal molecules (nucleic acids) (Fig. 1). Thus, many viruses can be treated via aPDT, including papillomavirus (HPV), hepatitis A virus (HAV), and herpes simplex virus (HSV) [54–56]. Additionally, the disinfection of biological fluids (plasma and blood products) by photoantimicrobials has been performed for decades and is a well-regarded technological application of these compounds. For instance, extracorporeal photoinactivation of coronaviruses and other clinically relevant pathogens using methylene blue (MB)-mediated aPDT has been reported [57–62].

It is possible that photosensitized oxidation can neutralize SARS-CoV-2 and, consequently, play a role in mitigating the ongoing pandemic; however, there is no data available on the photodynamic inactivation of this virus. Thus, here we sought to find and discuss scientific literature that could help predict whether COVID-19 is more or less susceptible to oxidant species generated during aPDT.

While all types of viruses can be neutralized by aPDT, the inactivation efficiency depends on both the PS and the virus [63,64]. As a rule of the thumb, RNA-type phages are more easily photoinactivated than their DNA-type counterparts, suggesting that SARS-CoV-2, which is an enveloped RNA-type virus, can be easily neutralized by aPDT [64,65]. Guanine bases are the major targets for oxidation by

photosensitizing agents in both RNA and DNA [66]. The formation of RNA-protein crosslinks may also be an important lesion involved in virus inactivation via aPDT [67].

Enveloped viruses are more prone to aPDT neutralization than those without an envelope, due to the role of PS in damaging envelope components [68,69]. Initial studies on viral inactivation by aPDT demonstrated the importance of the PS reaching specific reaction sites, so-called "marked targets", for efficient viral inactivation [70]. Other reports have confirmed the importance of PS binding on the efficiency of virus inactivation via aPDT, and the PS membrane partition coefficients can be used as a predictor of its virus inactivation efficacy [71,72]. Transmission electron microscopy data has revealed that low PS concentrations degrade envelope surface glycoproteins blocking virus internalization, while higher PS concentrations can destroy lipid membranes [73]. These results can be interpreted in terms of the current mechanistic understanding of photosensitized oxidation, specifically the important role of direct-contact reactions. Irreversible membrane damage occurs with the abstraction of a hydrogen atom from an unsaturated fatty acid by direct reaction with the triplet excited state of the PS. Subsequent formation of peroxyl and alkoxyl radicals leads to the build-up of truncated lipid aldehydes, which are ultimately responsible for opening membrane pores [74]. The fact that irreversible damage occurs due to contact-dependent reactions, indicates that the damage can be confined within the nanometer location site of the PS [75].

In terms of the application of aPDT to treat COVID-19 patients, it is encouraging to note that this technique is already used to treat several respiratory diseases [76]. PDT has been used for decades to treat lung cancers and its successful application in the treatment of laryngeal papillomas has also been reported [77]. Geralde *et al.* recently demonstrated that acute pneumonia caused by *Streptococcus pneumoniae* could be treated via inhalation of indocyanine green combined with extracorporeal administration of infrared light [78]. A prophylactic approach proposed by Soares *et al.* showed that aPDT can also be used to eliminate bacterial biofilms frequently associated with endotracheal tubes and that can lead to more severe stages of acute respiratory syndromes [79]. More recently, Schikora and colleagues reported succesfull use of aPDT to disinfect oral and nasal cavity of patients in early stages of COVID-19 infection This approach can potentially lead to a temporary and moderate reduction of disease progression but cannot be regarded as a potential therapeutic procedure since aPDT is limited to local effects and COVID-19 is a systemic disease [80].

Considering that: 1) SARS-CoV2 is an enveloped RNA virus, 2) aPDT is efficient at neutralizing such viruses, and 3) light is already used to treat lung and airway-related infections, we propose that aPDT is a good candidate for treating COVID-19 or as an adjunct to disinfect biological fluids. Alternatively, photosensitizers could also be used to decontaminate liquids and surfaces or be incorporated into polymeric matrices such as plastics, fabrics, paper, and paints to produce photoantimicrobial materials [53,58,81]. Allotropes of carbon such as fullerenes, carbon nanotubes, and graphene can also show light-activated antimicrobial effects, including the inactivation of viruses [69,82,83].

7. Antimicrobial Blue Light

Visible blue light exhibits microbicidal effects in the wavelength range of 405–470 nm [25,84–88]. High-intensity narrow-spectrum light at 405 nm has been used for continuous decontamination of inpatient and outpatient burn units and patient-occupied intensive care isolation rooms, as well as the treatment of surgical site infections in an orthopedic operating room [89–91]. Compared to UV-C, in general terms antimicrobial blue light (aBL) requires a much higher radiant exposure (or longer exposure times) to reach similar levels of microbial inactivation if irradiance of the light sources is similar. Even though aBL displays decreased deleterious effects on mammalian cells, one should avoid direct eye exposure because eye lens focuses visible light and overexposure can promote either flash blindness or retinal lesions.

The exact mechanisms underlying the antimicrobial effects of blue light are not yet completely understood but appear to involve the formation of short-lived reactive oxygen species (ROS) [92]. The most widely accepted view of the process posits that the photochemical mechanisms of aBL are based on light energy excitation of endogenous microbial intracellular light receptors (chromophores), such as porphyrins and flavins. Once excited, these receptors undergo energy transfer processes that lead to the generation of cytotoxic ROS which react with intracellular components resulting in photodamage and cell death by oxidative stress [93]. Since endogenous photoreceptors appear to be absent in viruses, the mechanisms by which aBL affects these pathogens remains unclear. However, it is currently known that: 1) the use of exogenous photosensitizers improves the efficiency of inactivation by blue light, and 2) the inactivation is more pronounced when viral particles are present in body fluids, *e.g.*, saliva, feces, and blood plasma, which contain photosensitive substances [94,95].

Accordingly, antimicrobial blue light has been explored in the treatment of infectious diseases and as a disinfection adjuvant in healthcare settings. Clinical trials have revealed the efficiency of aBL in the treatment of acne, *Helicobacter pylori* gastrointestinal infections, and dental infections [87,96–98]. aBL was recently shown to rescue mice from methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* wound infections [99,100]. Oral anaerobic periodontopathogenic bacteria (*Porphyromonas gingivalis*, *Prevotella intermedia*, and *P. nigrescens*) were also inhibited or completely eradicated under blue light irradiation [101,102].

In a recent bioinformatics study, SARS-CoV-2 infection was reported to be dependent on porphyrin, which it captures from human hemoglobin, resulting in altered heme metabolism [103]. However, the *in silico* methods used to obtain such results have been questioned by a commentary publication, putting into doubt wheter SARS-CoV-2 actually interacts with heme metabolism and accumulates porphyrins [103]. If this thesis is experimentally proven to be correct, aBL might be able to kill SARS-CoV-2 by photoexcitation of its acquired porphyrins. Thus, experimental studies are required to verify the potential of aBL to prevent and control COVID-19.

8. Photobiomodulation Therapy

Photobiomodulation (PBM) employs low levels of red or near-infrared (NIR) light to treat and heal wounds and injuries, reduce pain and inflammation, regenerate damaged tissue, and protect tissue at risk of dying [104]. Instead of directly targeting viruses, PBM mainly acts on the host cells, which absorb light in the red and near-infrared spectral region [104]. Literature indicates that photons are absorbed by multiple cellular chromophores, including mitochondrial enzymes, to trigger the biological effects of PBM [104–106]. Cytochrome c oxidase (*i.e.*, unit IV in the mitochondrial respiratory chain) appears to play a main role in this process [104]. Other molecular chromophores include light and heat-sensitive ion channels (transient receptor potential) that, upon light activation, lead to changes in calcium concentrations. Nanostructured water (interfacial water) is also likely to act as a chromophore. Upon irradiation, the mitochondrial membrane potential is raised and oxygen consumption and ATP generation are increased. Subsequent activation of signaling pathways and transcription factors leads to fairly long-lasting effects even after relatively brief exposure of the tissue to light [107].

In the early 1900s, Finsen reported that patients exposed to red light exhibited significantly better recovery from smallpox infections than unexposed counterparts [21]. Since then, PBM has been used in the treatment of acute lung injury, pulmonary inflammation, and models of acute respiratory distress syndrome (ARDS), due to its ability to substantially reduce systemic inflammation while preserving lung function. [108–110]. There are currently 90 published papers on PBM concerning "acute lung injury" [110] OR "pulmonary inflammation" [111] OR

Table 1
Light-based strategies available to combat the emergence of COVID-19 pandemic. FFR: filtering facepiece respirator.

Light-based Platform	Potential Applications	Advantages	Disavantages
Natural Ultraviolet Light		Synthesis of vitamin D Microbicidal activity	Sunburn following overexposure Long-term aging and cancer risk
Ultraviolet Germicidal Irradiation	Surface, FFR reuse, air and water disinfection	Low exposure time to reach high levels of pathogen inactivation (< 1 min) depending on irradiance of light source	Risk of tissue damage and cancer Potential long-term degradation of materials
Photoantimicrobials and Photodynamic Therapy	Environmental and surface disinfection, therapeutics, virus inactivation in biological products	Efficient and selective pathogen inactivation following short period of illumination if photosensitizer is resonant to light source wavelength Non-invasive approach Succesfull results in humans with artificial light sources	Photosensitizer could promote material and/or tissue staining Systemic PS administration may cause photosensitivity Succesfull results depend on light parameters, type of microorganism, PS concentration and pre-irradiation time
Antimicrobial Blue Light	Environmental and surface disinfection, therapeutics, virus inactivation in biological materials	Can be used in inhabited places and to treat infections in humans No notable detrimental effect in materials following long periods of illumination	Long exposure time (above 30 min) Effect is more pronounced in the presence of exogenous photoabsorbers
Photobiomodulation Therapy	Therapeutics	Non-invasive technique Succesfull results in humans with artificial light sources Adjuvant to conventional therapies	Succesfull results depend on light parameters, patient characteristics and disease aetiology
Ultrafast Laser Irradiation at low irradiance	Selective virus inactivation in blood products, pharmaceuticals, food and vaccine development	Selective pathogen inactivation Chemical-free vaccine preparation	Long exposure time (3 h) Expensive light sources

"lung inflammation" [109] OR "ARDS" [112] OR "lung oxidative stress" [113] OR "asthma" [114] many involving small animal models where it can be argued that light penetrates more easily than in humans. Because COVID-19 involves a "cytokine storm", PBM delivered to the torso (chest and back) might not only allow some light to reach the lungs but might also reduce the systemic inflammation responsible for COVID-19 sepsis-like syndrome [115] and disseminated intravascular coagulation [116] that can be deadly [117]. Moreover, PBM is more effective on hypoxic cells [118], suggesting it could be effective for COVID-19 infection, which seems to be characterized by severe hypoxia [119]. Nevertheless, so far there are no experimental data supporting the influence of PBM on COVID-19. Therefore, clinical studies have to be performed to understand whether PBM therapy may actually reduce the cytokine storm impacts for COVID-19 patients.

Hospitalized patients receiving mechanical ventilation or under high-oxygen continuous positive airway pressure (CPAP) treatment could be placed on an LED pad. These do not generate unacceptable levels of heat, so the high fever experienced by these patients should not be a problem. LED-based PBM devices similar to these have been approved by the FDA for general health and wellness applications, and there are no reported adverse effects [120]. However, PBM is not recommended to be used over cancerous lesions since the effects on tumor cells are not fully understood yet [121].

9. Ultrafast Laser Irradiation

Ultrashort pulse lasers (USPLs) emitting visible to near-infrared light have been used to inactivate a broad spectrum of viruses (human immunodeficiency virus, human papillomavirus, encephalomyocarditis virus, M13 bacteriophage, tobacco mosaic virus, and murine cytomegalovirus) with no damage to human or murine cells [122–126]. Regardless of wavelength, ultrafast laser irradiation at low mean irradiance levels ($\leq$ 1 W/cm^2) does not promote ionization effects that could impair host cells. This irradiation does not appear to destroy either bovine serum albumin or single-stranded DNA, nor cause adverse effects like those produced by toxic or carcinogenic chemicals. Previous works suggest that the antimicrobial effect of USPLs at low mean irradiance is exerted via impulsive stimulated Raman scattering, whereby high-frequency resonance vibrations provoke vibrations of sufficient strength to disintegrate the capsid into subunits through the breaking of weak links (*e.g.,* hydrogen bonds and hydrophobic contacts) in non-enveloped viruses [126]. For enveloped virus, USPLs promote vibrations on the proteins of the capsid. These excitations break the hydrogen bonds and hydrophobic contacts causing partial unfolding of the proteins. Since the concentration of confined proteins is very high within the capsid of a virus, they can assemble with other neighboring proteins, leading to the aggregation of proteins [125]. In contrast, an intense laser pulse could generate shock wave-like vibrations upon impact with the virus to promote viral inactivation [126].

However, laser pulsing may not be necessary for its antimicrobial action. Recently, Kingsley *et al.* applied a tunable mode-locked Ti-Sapphire laser emitting femtosecond pulses at wavelengths of 400, 408, 425, 450, 465, and 510 nm to verify inactivation of murine norovirus (MNV) [92]. Using an average power of 150 mW, authors observed that femtosecond-pulsed light emitting at 408, 425 and 450 nm promoted more than 99.9% of virus inactivation after 3 h of illumination, indicating that the inactivation mechanism is not wavelength-specific. In addition, they reported that a continuous wave 408 nm laser at similar power also promoted reduction of plaque-forming units, although the addition of exogenous photosensitizers has increased MNV inactivation. These data suggest that virus inactivation does not require pulsing and can be improved in the presence of singlet oxygen enhancers, as previously reported for aBL (see section 7).

Potential use of USPLs encompasses the inactivation of pathogens in pharmaceuticals, blood products and uncooked foods as well as chemical-free whole inactivated virus vaccine preparation [127,128]. Laser treatment resulted in 1-log, 2-log, and 3-log reductions in hepatitis A, human immunodeficiency, and murine cytomegalovirus, respectively, in human plasma with no changes in the structure of fibrinogen [127]. Further, in mice USPL-induced inactivation of H1N1 influenza virus was more effective than formalin and did not cause damage to viral surface proteins or resulted in the production of carbonyl groups in proteins [128].

Concluding remarks

As we presented in this review, light-based technologies have unique features that could be useful to face the COVID-19 pandemic, but could also present pitfalls that deserve to be highlighted. Thus, we compiled at Table 1 their advantages and disadvantages.

In summary, we have described how light-based strategies can be used to reduce SARS-CoV-2 transmission through air, water, and

surfaces as well as potential therapeutic applications that can reduce COVID-19 morbidity and mortality. From our perspective, light provides several practical answers to the new logistical and therapeutic challenges brought by COVID-19. Therefore, we suggest that the death toll and quarantine extent can be significantly mitigated if at least part of these strategies are encouraged and implemented by health systems. Given the urgent demand raised by the current uncontrolled pandemic we must be ready to use all the available armamentarium to fight COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

We attest no conflict of interest in the manuscript we are submitting entitled "Antimicrobial light-based technologies for management of COVID-19 pandemic crisis".

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