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Topical Review

An update on clinical photodynamic therapy for fighting respiratory tract infections: a promising tool against COVID-19 and its co-infections

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Abstract

Recently coronavirus infection 2019 (COVID-19) was declared as a Public Health Emergency by the World Health Organization. Extensive measures to reduce person-to-person transmission of COVID-19 and scientific research have been developed aiming to combat it. The idealization of vaccines will be of great help, but they will have to be constantly redone due to the high frequency of mutation of the virus. Also, it is necessary to develop techniques that allow to combat viral, bacterial and fungi load. In this sense, photodynamic therapy can be an alternative and efficient tool against viruses, bacteria, and fungi in the respiratory tract. The photodynamic therapy protocol is characterized by activation of a photosensitizer using an appropriate light source that in the presence of molecular oxygen is able to damage microorganisms. Herein, we review the past 25 years (1995–2019) concerning the use of photodynamic therapy in clinical trial against respiratory tract infections. We did not intend to create a comprehensive review; instead we highlight some the most important aspects for this infection to connect with the possibility of inactivation of the SARS-CoV-2 and its co-infections by photo reaction. We emphasize the use of photodynamic therapy as a potential clinical tool to decrease the microbial load in the respiratory tract, showing its main applications, advantages, and limitations.

Keywords: coronavirus infection 2019, SARS-CoV-2, severe acute respiratory syndrome, infection, respiratory tract, photodynamic therapy

(Some figures may appear in colour only in the online journal)

1. Introduction

Ancient civilizations (~3000 BC) already applied sunlight against various skin diseases. Possibly this was the first clinical protocol involving light interaction with biological tissues, however, in an empirical way [1, 2]. Along the years, the application of light, molecular oxygen (O_2) and a photosensitizing molecule (PS) has improved and has emerged the called '*Photodynamic therapy (PDT)*'. It is a well-established and non-invasive treatment applied against cancer and many infections [3–5] such as the current security situation (with respect to bioterrorism, recurring military and disaster scenarios), food safety, viral infections [6] as well as aiming to address the antibiotic resistance [7].

The photodynamic protocol is well-defined by an oxygen-dependent processes that in the presence of light–mediated

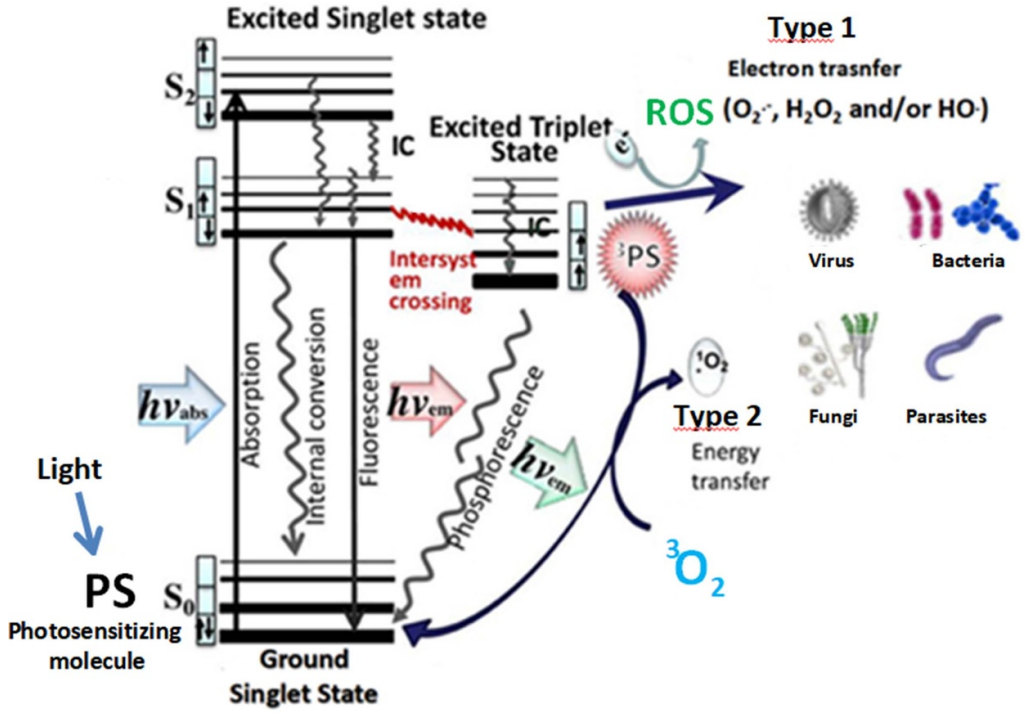

Figure 1. General mechanism of photodynamic action illustrated by Jablonski's diagram. Adapted from reference [11]. Copyright 2018 Frontiers.

activation of a photosensitizing molecule yielding cytotoxic reactive oxygen species (ROS) [8] that are able to damage microorganisms. In this context, this therapy has been used in the treatment of cancer, bacterial, viruses, and fungal infections, and also in the photodynamic diagnosis in dentistry field [9].

The details of mechanism of photodynamic action is illustrated by Jablonski's diagram (figure 1), which is defined by several photochemical and photophysical reactions through light absorption, energy/electron transfer and proton abstraction [10].

From the analysis of Jablonski´s diagram (figure 1), the photosensitizing molecule in its ground singlet state has two electrons (opposite spins) and the total spin is zero (with the symbol S0). When a PS is excited by a light with an appropriate wavelength (quantum energy) results to the excitation of one electron into a higher-energy orbital, called 'excited singlet state' (S1). In this step, the singlet excited-state may loses its energy by internal conversion producing heat or emission of light through fluorescence process. Furthermore, the higher-energy orbital (excited singlet state—S1) may suffer an intersystem crossing (IC) resulting in a more stable excited triplet state (parallel spins). Then, the excited triplet state shows a life time of microseconds (higher than exited singlet state) which may undergo to the ground singlet state emitting a phosphorescent photon or transfer electron to O_2 (type I mechanism) resulting on formation of reactive oxygen species (ROS) such as superoxide radical anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($HO^{\bullet}$) or transfer energy to O_2 (type II mechanism) yielding singlet oxygen ($^1O_2$). These ROS and $^1O_2$ formed can combat pathogenic microorganisms, for example viruses, bacteria, fungi, and parasites [11–13].

2. The current challenge—coronavirus infection 2019 (COVID-19) outbreak

Severe acute respiratory syndrome (SARS), COVID-19, is caused by SARS-CoV-2 (named by The International Committee on Taxonomy of Viruses (ICTV) (figure 2). Four coronavirus genera (α, β, σ, γ) were identified so far, with human coronaviruses (HCoVs) detected in the α-coronavirus (HCoV-229E and NL63) and β-coronavirus (MERS-CoV, SARS-CoV, HCoV-OC43 and HCoV-HKU1) genera [14]. In that case, the SARS-CoV-2, is a type of β-coronavirus that possess a single-stranded ribonucleic acid (RNA) as nuclear material that belongs to the Coronavirinae subfamily, part of the Coronaviridae family. Its genome has been correlated to an identified coronavirus strain that resulted the SARS-CoV outbreak in 2003 [15]. So far 2003, these type of viruses were thought to infect only animals [16].

At the end of 2019, in a seafood market in Wuhan (China) which is known by the sale of live animals like bats, frogs, snakes, birds, marmots and rabbits [17] experienced an outbreak of a novel coronavirus that was called as SARS-CoV-2. This episode was marked by a series of catastrophic events. The National Health Commission of China released further details about a new epidemic, suggested viral pneumonia [17]. Then, after sequence-based analysis of infected patients and genetic sequence studies, a novel coronavirus (SARS-CoV-2) was identified. Moreover, researchers suggested that after genomic similarity findings of novel coronavirus with

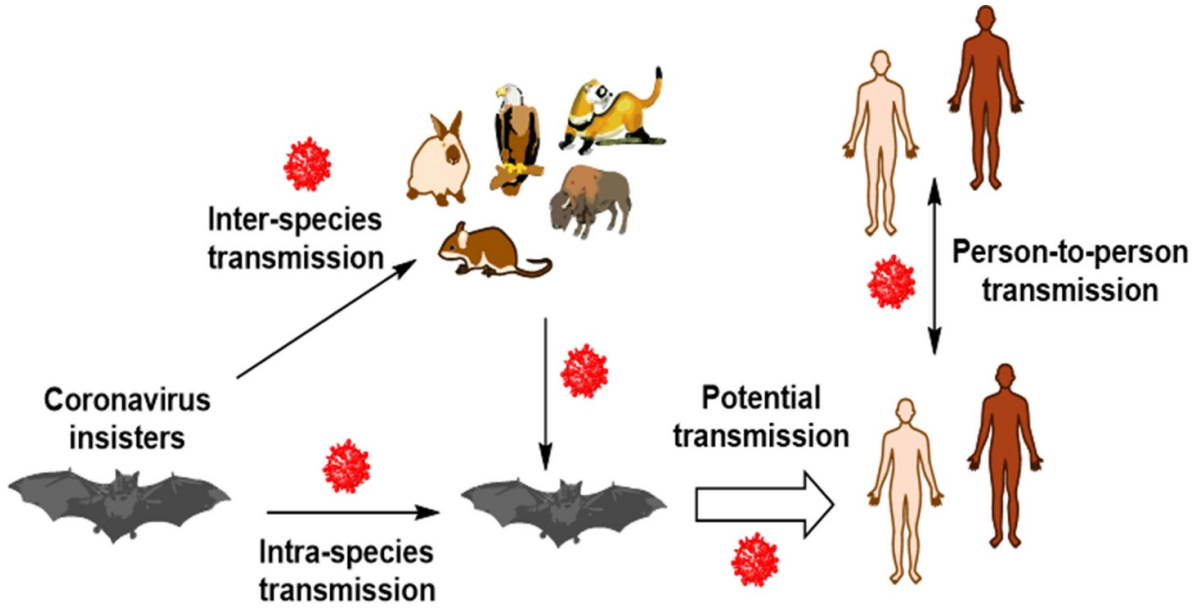

Figure 2. The potential key reservoirs and mode of transmission of SARS-CoV-2.

SARS-like bat viruses supported that only bats could be the key reservoirs [18]. The origin and transmission pathways are fundamental to be determined in order to develop preventive strategies to fight an infection. In that specific case, it was suggested that patients were infected and induced pneumonia due to a visit in a seafood market which containing infected animals, like bat, that are traditionally used as source of food. However, studies revealed that some patients obtained COVID-19 with no record of visiting the seafood market, indicating that person-to-person transmission occurs, which was subsequently reported worldwide [19] (figure 2).

So far, there are no approved/specific antiviral drugs or vaccine against COVID-19 infection [20]. Antipyretic drugs e.g. paracetamol has been intensively used for the first-line treatment against fevers, whilst expectorants (e.g. guaifenesin) may be used for a non-productive cough [21]. Patients that showed severe acute respiratory infection, respiratory distress, hypoxaemia or shock must be applied oxygen therapy. To avoid further bacterial and/or fungal infections during the middle and latter stages of the COVID-19 disease, broad spectrum antibiotic therapy have been used [22, 23]. Furthermore, there are many ongoing researchers around the world aiming to develop antiviral drugs and vaccines against COVID-19, since the only options available is using broad-spectrum antiviral drugs like lopinavir/ritonavir (Kaletra®), nucleoside analogs, neuraminidase inhibitors, remdesivir, umifenovir (arbidol), DNA synthesis inhibitors (such as tenofovirdisoproxil, and lamivudine), chloroquine, ACE2-based peptides, 3 C-like protease (3CLpro) inhibitors, novel vinylsulfone protease inhibitor [24–31]. A report showed that the broad-spectrum antiviral remdesivir was effective to combat COVID-19 infection infection *in vitro* (EC50 = 0.77 mM and EC90 = 1.76 mM in Vero E6 cells) [25]. In a clinical report, the administration of corticosteroids was not recommended in the interim, unless indicated for another reason, such as for patients that show severe immune reactions [32].

In addition, passive immunization therapy and the use of interferon could be helpful, but to date there is no clinical or scientific evidences to validate this hypothesis [33]. Other potential strategies have been studied, Chinese doctors isolated the blood plasma from clinically recovered patients and injected into infected patients who showed positive for COVID-19 showing a rapid recovery [34]. And recently, some authors hypothesized that vaccines for other diseases such as rubella or measles can create cross-resistance for SARS-CoV-2. This statement was based on the clinical observations that children in China and other countries are more resistant to COVID-19 when compared to the elder population. It could be due to children were largely vaccinated for measles worldwide [35].

I sum, it is clear that more research is urgently required on development of an alternative and effective therapy against COVID-19 infection, its co-infections, and future outbreaks.

3. Photodynamic therapy for the treatment of infections

Infections disease is one of the most serious public health problems that multidisciplinary research teams are working on [36, 37]. The number of new antimicrobial and their targeted structures have continuously decreased emphasizing the demand of alternative therapy for infections. Photodynamic therapy is such a promising and alternative tool that has been proven to be effective against a wide range of microorganism's strains [38–40].

3.1. Viral, bacterial and fungal targets in a photodynamic protocol

Firstly photodynamic inactivation protocol to combat virus was reported in 1928 [41], followed by clinical treatment of herpes infection in the United States, in 1970 s [42]. Similarly

Table 1. Parameters of cellular basis for photovirucidal action [46].

Site of action	Chemical Reaction	Photoreaction results	Virucidal event
Water	Hydrogen abstraction	Formation of ($HO^{\cdot}$), H_2O_2 and (O_2^{-})	Further oxidative processes
Envelope: unsatured lipids	Peroxidation	Peroxidation and hydroperoxide formation	Increased ion permeability (Na^+/ K^+ leakage)
Viral protein coat	Hydrogen abstraction	Peptide cross-linking and enzyme inactivation	Loss of repair facility, lysis
Protein coat	Oxidation of Try/Met/ His residues	Protein degradation	Loss of viral infectivity
Enzymes (e.g. reverse transcriptase)	Oxidation or crosslinking (as above)	–	Inhibition of ribosome assembly, inhibition of replication/infectivity
Nucleic acid residues (typically guanosine)	Oxidation of base or sugar	Nucleotide degradation Sugar degradation/cleavage	Base substitution, strand cleavage, mutation, inhibition of replication

to application of PDT against cancer, photodynamic inactivation of virus display the general mechanism described in figure 1, where a photosensitizer is irradiated with an appropriated source light resulting on generation of ROS and $^1O_2$ which are able to promote damaging of virus targets by reacting with viral nucleic acids, lipids and/or proteins [43]. This non-specificity against the viral targets observed in a photodynamic protocol is considered one of most important advantages when compared to others anti-viral drugs. It can overcome the genetic flexibility of viruses preventing the development of resistance in the target entity [44]. To be effective, the PS used for viral PDT must specifically bind to vital viral components, such as a lipid envelope (when present), protein coating or nucleic acids [45]. Thus, in 2003, Prof. Wainwright reported useful parameters describing cellular basis of photovirucidal action showing a correlation between site of action, mode of action, result, consequence, and virucidal molecular event (table 1).

From the analysis of table 1, Type I mechanism (electron transfer and/or proton abstraction) resulting on formation of ROS e.g. superoxide radical anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($HO^{\bullet}$). These ROS can promote the abstraction of allylic hydrogens from phospholipids, formation of lipid hydroperoxide, aminolipids and/or peptides. Moreover, cell envelope can be oxidized yielding the inactivation of enzymes and receptors as well as peroxidation of lipid can destroy structural integrity of a virus, increasing ion permeability (Na^+ and/or K^+) [47]. On other hand, Type II mechanism (energy transfer) is considered the most effective against viruses. In that case, singlet oxygen ($^1O_2$) react with molecules presented in the external structure of the cell, for instance amino acid tryptophan and methionine residues [48].

In this sense, PDT against viruses has been used in clinical protocols against localized viral lesions such as herpes and warts [49, 50]. Additionally, it has showed potential in extracorporeal applications e.g. disinfection of blood products (viruses transmitted through blood products and transfusions include CMV (cytomegalovirus), B19 (human parvovirus), human T-cell lymphotropic virus, HAV (hepatitis A virus), HBV (hepatitis B virus), HCV (hepatitis virus), and HIV (human immunodeficiency virus), decontamination of surface [51] and for inactivation of virus for production of vaccines [52]. A wide examples regarding the use of photodynamic therapy against viruses was recently reported by Wiehe, O'Brien, and Senge [43]. In this perspective paper, the authors described current viral targets, design and synthesis of photosensitizers, and the application of different photosensitizers in PDI of viruses and their various areas of use (purification of blood products, treatment of human papilloma virus, water and surface decontamination, and biosafety).

Regarding bacteria, there are two main targets/mechanisms for their lethal processes caused by photodynamic therapy: i) DNA damage; ii) damage to the cytoplasmic membrane, which allows leakage of cellular components or by inactivation of membrane transport systems and enzymes [53]. Moreover, there are a fundamental difference in susceptibility of Gram-positive and Gram-negative bacteria when they have submitted to a photodynamic protocol. In general, high susceptibility of Gram-positive species is observed which can be explained by their physiology/structure, as their cytoplasmic membrane is surrounded by a relatively porous layer of peptidoglycan and lipoteichoic acid that allows photosensitizer to cross. On the other hand, the cell envelope of Gram-negative bacteria present of an inner cytoplasmic membrane and an outer membrane forming a physical and functional barrier between the cell and its environment [54].

It has been described that the mechanism of photodynamic action is multi-factorial and non-specific. In this regard, the application of PDT against fungi is an area of increasing interest. It involves the damage of fungal cell wall and/or membrane [55] through oxidation of enzymes, proteins, lipids, and/or mitochondria causing cell death. Dentistry field is one of the most applied area of PDT against fungi due to the accessibility of the oral cavity and excellent results have been reported [56, 57].

Overall, given efficacy of PDT against viruses and other microorganisms reported in the literature as well as the low probability of resistance formation due to the non-selective nature, the photodynamic therapy is really a potential weapon against the SARS-CoV-2. A large variety of work has demonstrated the efficacy of photodynamic action in viruses inactivation such as MVM (minute virus of mice),

poliovirus, HSV-1 (herpes simplex virus 1), SFV (semliki forest virus), VSV (vesicular stomatitis virus), HIV-1 (human immunodeficiency virus 1), HRV (human rhinovirus), WNV (West Nile virus), SIV (simian immunodeficiency virus), INF (influenza virus), and HPV (human papilloma virus) [52, 58–61]. To those lodged in the cells, they may also be inactivated by the selectivity that the viruses present concerning the adherence to certain molecules like photosensitizers.

3.2. Photodynamic therapy: a clinical reality in the treatment of respiratory tract infections

The entrance of particulate material into the respiratory tract including living organisms is capable of producing several types of respiratory diseases. Thus, the nose acts as an air filter but only particles larger than 10 μ in diameter tend to be filtrated [62]. It is importance to emphases that the majority of particles less than 10 μ passing through the nose into the larynx, trachea, bronchi, and lungs by airflow and/or liquids secretions. Thus, the accumulation of secretions possessing pathogenic microorganisms in the oral pharynx can be aspirated *via* liquid-phase into the lungs resulting in the development of an infection or a co-infection in the case of COVID-19. In this regard, we believe and emphasizes that the PDT can be a useful tool to decrease the microbial load in the respiratory tract (nasal cavity, pharynx, larynx, trachea, bronchus, bronchiole, and lungs) avoiding the development of an infection and/or a co-infection.

One of most serious symptoms in COVID-19 infection is pneumonia (viral and/or bacterial). So, dual correlated infections could either be viral-viral or viral-bacterial as the human respiratory tract is a reservoir for many organisms. At the host level, the outcome of dual infection is commonly viral interference, such as when one virus competitively inhibits the replication of another virus, but it can also enhance replication in some cases [63] altering the epidemiology of viral infections. It is postulated that the sequence of infections, the time interval between viral exposure, and the route of infection affect the pathogenicity of the co-infection.

To date, there are many *in vitro* and animal studies applying PDT for combating respiratory tract infections that can be considered good start points [64–66]. Moreover, an increasing interest have been observed on use of clinical PDT protocols against infections in the respiratory tract. Thus, a comprehensive review of the past 25 years (1995–2019) concerning the use of photodynamic therapy in clinical trial against respiratory tract infection will be described and discussed. In figure 3 is summarized the regions of respiratory tract that have been clinically treated with PDT.

In 2005, Shikowitz and co-authors [67] evaluated the use of *meso*-tetra (hydroxyphenyl) chlorin (*m*-THPC) as photosensitizer for the treatment of recurrent respiratory papillomatosis and also if a single adjunct PDT protocol reduces the frequency of recurrent disease compared to surgery alone. In this study, randomized trial of patients requiring surgery at least 3 times yearly with single PDT 6 or 18 months after enrollment and 12-month follow up were evaluated. For the PDT protocol, a source light at 652 and a light dose ranged from 80 to 100 J for adults and 60 to 80 J for children were used. The authors observed that: (i) tracheal disease was not responsive to PDT; (ii) no change occurred in the prevalence of latent human papillomavirus DNA; (iii) the immune response to virus improved with clinical response. Thus, the application of photodynamic protocol showed a significant efficacy in the treatment of papillomatosis in the larynx, probably reflecting improvement in the immune response by indirectly immunizing the patient to HPV proteins.

In 2011, Donelly [64] reported a preliminary photodynamic protocol using methylene blue as photosensitizer and an *ex vivo* and *in vitro* lung model aiming to investigate the delivery of light (at 635 nm) and methylene blue to the lung. Using a fiber-optic light, up to 11% of the total light dose penetrated through full thickness pulmonary parenchymal tissue, which indicates potential for multiple lobe irradiation *in vivo*. The mass median aerodynamic diameter of particles generated via methylene blue solution nebulization was 4.40 μm, which is suitable for targeting the site of infection within the cystic fibrosis lung. The authors observed that planktonic and biofilm cultured CF pathogens have proven to be highly susceptible to photodynamic protocol used, being considered a clinical option for selective killing of cystic fibrosis lung pathogens.

In 2014, Zhou and collaborators reported the treatment of laryngeal papillomatosis in children using a clinical photodynamic protocol [68]. For this treatment, the authors used a commercial solution of aminolevulinic acid hydrochloride (topical powder, 3 to 5 bottles, 118 mg per bottle, Fudanzhangjiang Bio-Pharmaceutical, Co, Ltd, Shanghai, China) and a laser with an illumination source at 635 nm showing a power of 280 to 300 mW. A cotton ball was immersed in the photosensitizer solution and placed on the surface of the infected region, with a fresh solution re-applied to the cotton ball every 30 min followed by photoactivation at 635 nm with a light dose of 100–200 J cm^{-2}. A return visit was made 1 to 2 weeks after the treatment, and PDT was done again if recession of the mucosa edema was observed. The authors reported that this protocol was able in all cases applied removing the virus from mucosa without systemic side effects.

In 2014, Lieder, Khan, and Lippert reported a review paper [69] regarding the use of photodynamic therapy against recurrent respiratory papillomatosis. In this well-documented paper, the authors randomized controlled trials utilizing photodynamic therapy as sole or adjuvant therapy in participants of any age with proven recurrent respiratory papillomatosis versus control intervention.

In 2016, Zhang and co-authors [70] reported the application of 5-aminolevulinic acid as photosensitizer via self-retaining laryngoscope combined with CO_2 Laser Therapy to treat three patients with juvenile laryngeal papilloma. This infection disease is a type of common benign tumor occurring in children's throats, which is mostly related to the infection with Human Papilloma Virus (HPV). Their laryngeal papillomas were distributed either in rear pharynx wall, right laryngeal ventricle, right vocal cord, or below glottis. After PDT treatment

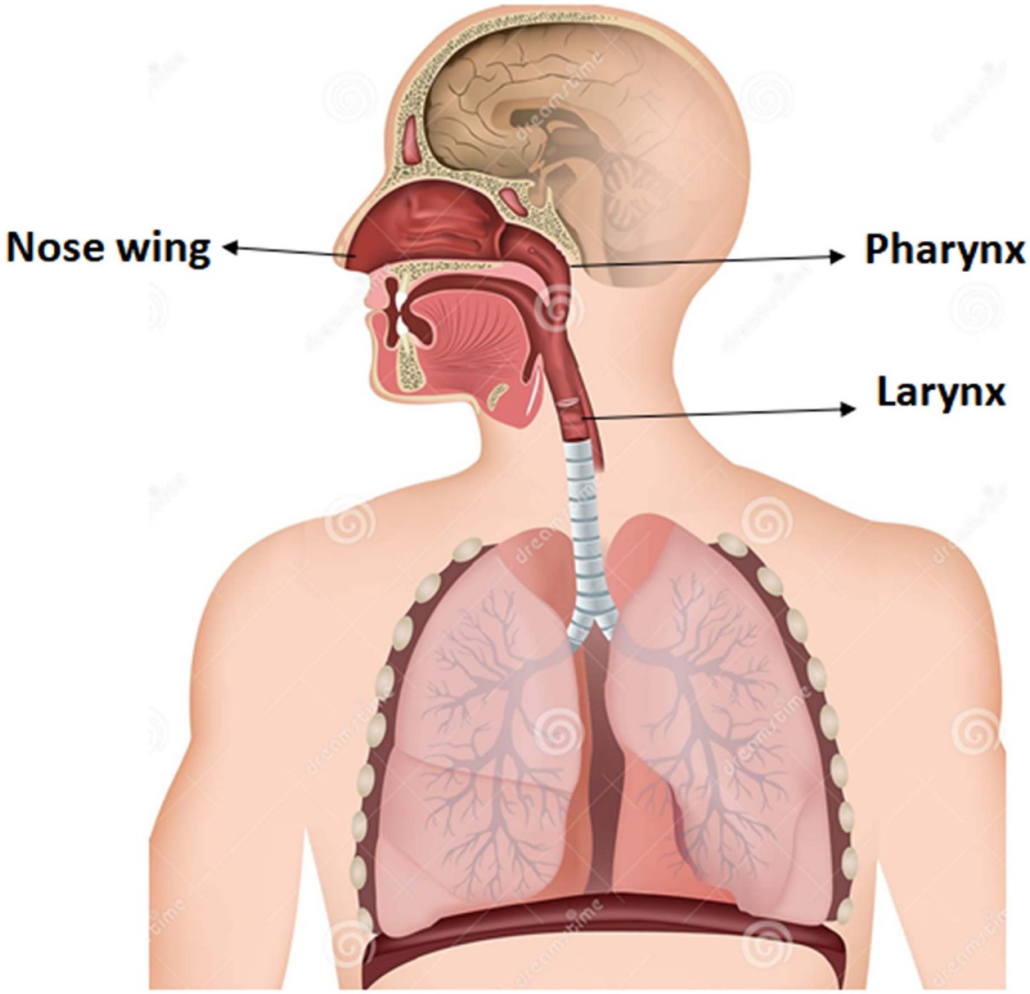

Figure 3. Schematic figure of the respiratory tract regions that have been clinically treated with PDT.

(at 635 nm and a light dose of 100–120 J cm^{-2}) combined with CO_2 Laser Therapy, the authors observed that laryngeal papilloma was fully eliminated from the three patients, with no recurrence during the 6–24 months of follow-up medical examination.

In 2017, Blanco and co-authors [71] reported the use of PDT against pharyngo-tonsillitis which shows a high incidence in children and young people. In this clinical report, a patient with confirmed diagnosis of infection and inflammation of the pharynges was submitted to a photodynamic therapy protocol. Before that, ten recurrent times infection occurred and a standard treatment with lyophilized bacterial, azithromycin, amoxicillin and anti-inflammatory was administered to patient. Regarding the PDT protocol used, three gargles (30 s each) of curcumin (0.75 mg ml^{-1}) as photosensitizer and the oropharynx was illuminated using a homemade device at 450 nm, showing a light dose of 2.2 J cm^{-2}. Then, others sections was performed using the same parameters. The authors observed a bacterial reduction after first section. This case report was part of a complete research that involved 72 patients with absence of signs of disease after 24 h from PDT and reduction (average) of 1 Log of bacteria after illumination. Moreover, due to it is applied locally, it has minimal side effects, and a repetition of procedure causes no extra concern.

In 2017, Blanco and co-authors [72] also reported two case reports on use of a gum containing curcumin photosensitizer and its application in clinical PDT protocol against pharyngo-tonsillitis. This innovative pharmaceutical formulation was able to deliver curcumin photosensitizer into tonsils and pharynx. For both cases, a microbial reduction of 1 Log_{10} of CFU after the treatment and no recolonization after 24 h were achieved.

In 2018, Lago and co-authors [73] described a clinical study using PDT and its association with photobiomodulation aiming to combat herpes simplex in the nose wing region. In this work, a 19-year-old female patient showed a clinical diagnosis of HSV-1 in the vesicle phase due to the clinical characteristics, anatomical position affected, and her history. After all vesicles had been ruptured, a PDT protocol using a solution of methylene blue (0.01% w/v) as photosensitizer and a light dose (at 660 nm) of 12 J cm^{-2} was performed. According to patient a significant improvement in itching and burning after the first PDT section was observed. After 24 h, a photobiomodulation therapy (75 J cm^{-2}) was carried stimulating more organized collagen fibers and favoring the reduction of tissue

repair time. The authors concluded that the combination of PDT and photobiomodulation was effective as a treatment of herpes simplex in the nose wing region.

Moreover, one way of delivering drugs (photosensitizer) directly to the respiratory system is via nebulization. This route of administration can overcome drug delivery problems, decreasing the side effects generated by intravenous injection and, in the case of photodynamic inactivation, delivering photosensitizers directly to the lungs [74]. In 2016, Geralde and co-authors [75] developed a proof-of-principle protocol to treat lung infections by a photodynamic protocol using extracorporeal illumination (at 780 nm) using indocyanine green as photosensitizer. In this study, hairless mice were infected with *S. pneumoniae* and PDT experiment (120 J cm^{-2}) was performed two days after infection using an extracorporeal illumination approach. The authors observed no deaths occurred in PDT group, whereas 60% of the control group died. These results indicate that extracorporeal photodynamic protocol is a potential tool against pneumonia, and pulmonary decontamination with PDT may be used as a single therapy or as an antibiotics adjuvant.

The evolution of antimicrobial PDT as an alternative method for inactivating several microorganisms is mainly due to the fact that this treatment is not target-specific, therefore, it is considered incapable of generating resistance to target cells [76, 77]. Hamblin and Hasan [78] reported the photoinactivation of viruses *in vitro* and observed that viruses surrounded by lipids are more susceptible to PDT than non-enveloped strains. In this sense, the action and efficiency of photodynamic protocol will depend on photosensitizer molecular structure and the physical-chemical reactions with the structures of the target cell. In addition, PDT against viruses is equally effective if the virus is sensitive or resistant to conventional antiviral agents [77].

Despite of many clinical applications and advantages on the use of PDT against microorganisms, we hypothesize and expect that the photodynamic therapy can be a tool against COVID-19 and future outbreaks through decreasing the microbial load in the respiratory tract.

4. Conclusion and future directions

The COVID-19 outbreak is quickly increasing in number of cases and deaths worldwide. We are facing many unknowns, and monitoring and research should continue. The coming days/weeks will provide an enormous amount of new scientific data about SARS-CoV-2 which will allow us to make decisions for new treatment strategies. To date, effective treatment for SARS-CoV-2 is still lacking; however, two studies with potential drugs (remdesivir and chloroquine) are underway in China and US, and many pharmaceutical companies (e.g. Moderna Therapeutics, Inovio Pharmaceuticals, Johnson & Johnson, and others) are working for the development of effective vaccines to combat the SARS-CoV-2.

In this context, we hypothesize and expect that the photodynamic therapy may be an alternative and powerful tool against COVID-19 through decreasing the microbial load in the respiratory tract. There are studies in the literature showing photoinactivation of viruses for purification of blood products and for the treatment of human papilloma virus. Besides, there are advantages to be gained by such an approach over antiviral drugs and there are available photosensitizers and technological advances that allow to apply this therapy in the clinic against COVID-19. Despite of many applications and advantages of PDT against virus, some parameters still need to be studied, optimized, and well understand: (i) the correlation between photodynamic therapy and the immune system; (ii) the capacity of light and photosensitizer alone to tract virus infection; iii) the relationship between a photo inactivated viruses and the producing of an immune response; (iv) enveloped viruses have been shown to be significantly more sensitive to photodynamic destruction than non-enveloped viruses. Furthermore, regarding the use of animal as models for studies, the human ACE2 cell receptor is known by SARS-CoV-2. Thus, TALEN or CRISPR-mediated genetically modified hamsters or other small animals could be used for the study of the pathogenicity of COVID-19. In sum, we believe and expect that to overcome the COVID-19 infection and become preparing to future outbreaks, the coordination between public and private sector, and researchers (chemists, physics, biologists, pharmacologists, doctors) will be the drive force.

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Compliance with ethical standards

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

References

[1] Lai J and Cooney M 1999 History of photodynamic therapy *Int. Ophthalmol. Clin.* **39** 163–74
[2] Ackroyd R, Kelty C, Brown N and Reed M 2001 The history of photodetection and photodynamic therapy *Photochem. Photobiol.* **74** 656–69
[3] Kashef N, Huang Y Y and Hamblin M R 2017 Advances in antimicrobial photodynamic inactivation at the nanoscale *Nanophotonics* **6** 853–79
[4] Glueck M, Hamminger C, Fefer M, Liu J and Plaetzer K 2019 Save the crop: photodynamic Inactivation of plant pathogens I: bacteria *Photochem. Photobiol. Sci.* **18** 1700–8
[5] Maisch T, Szeimies R M, Jori G and Abels C 2004 Antibacterial photodynamic therapy in dermatology *Photochem. Photobiol. Sci.* **3** 907–17

[6] Kielmann M, Prior C and Senge M O 2018 Porphyrins in troubled times: a spotlight on porphyrins and their metal complexes for explosives testing and CBRN defense *New J. Chem.* **42** 7529–50

[7] Maisch T 2009 A new strategy to destroy antibiotic resistant microorganisms: antimicrobial photodynamic treatment *Mini-Rev. Med. Chem.* **9** 974–83

[8] Agostinis P *et al* 2011 Photodynamic therapy of cancer: an update *CA-Cancer J. Clin.* **61** 250–81

[9] Carrera E T, Dias H B, Corbi S C T, Marcantonio R A C, Bernardi A C A, Bagnato V S, Hamblin M R and Rastelli A N S 2016 The application of antimicrobial photodynamic therapy (aPDT) in dentistry: a critical review *Laser Phys.* **26** 123001

[10] Dabrowski J M 2017 *Advances in Inorganic Chemistry: Inorganic Reaction Mechanisms* Vol 70 ed R VanEldik and C D Hubbard (San Diego: Elsevier Academic Press Inc) pp 343–94

[11] Hu X Q, Huang Y Y, Wang Y G, Wang X Y and Hamblin M R 2018 Antimicrobial photodynamic therapy to control clinically relevant biofilm infections *Front. Microbiol.* **9** 24

[12] Castano A P, Demidova T N and Hamblin M R 2004 Mechanisms in photodynamic therapy: part one-photosensitizers, photochemistry and cellular localization *Photodiagn. Photodyn. Ther.* **1** 279–93

[13] Robertson C A, Evans D H and Abraharnse H 2009 Photodynamic therapy (PDT): A short review on cellular mechanisms and cancer research applications for PDT *J. Photochem. Photobiol.* B **96** 1–8

[14] Perlman S and Netland J 2009 Coronaviruses post-SARS: update on replication and pathogenesis *Nat. Rev. Microbiol.* **7** 439–50

[15] Lu R J *et al* 2020 Genomic characterisation and epidemiology of 2019. novel coronavirus: implications for virus origins and receptor binding *Lancet* **395** 565–74

[16] Cheng V C C, Lau S K P, Woo P C Y and Yuen K Y 2007 Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection *Clin. Microbiol. Rev.* **20** 660–94

[17] Wang C, Horby P W, Hayden F G and Gao G F 2020 A novel coronavirus outbreak of global health concern *Lancet* **395** 470–3

[18] Chan J F W *et al* 2020 A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster *Lancet* **395** 514–23

[19] Shereenab M A, Khana S, Kazmic A, Bashira N and Siddiquea R 2020 COVID-19 infection: origin, transmission, and characteristics of human coronaviruses *J. Adv. Res.* **24** 91–8

[20] Rothana H A and Byrareddy S N 2020 The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak *J. Autoimmun.*

[21] Wang D, Hu B and Hu C 2020 Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in wuhan, China *J. Am. Med. Assoc.* **323** 1061–9

[22] Rhodes A *et al* 2017 Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016 *Crit. Care Med.* **45** 486–552

[23] Kui L, Fang -Y-Y and Deng Y 2020 Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei province *Chin. Med. J.* **133** 1025–31

[24] L H 2020 Drug treatment options for the 2019-new coronavirus (2019-nCoV) *Biosci. Trends* **14** 69–71

[25] Wang M L *et al* 2020 Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro *Cell Res.* **30** 269–71

[26] Morse J S, Lalonde T, Xu S Q and Liu W R 2020 Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV *Chem3Bio Chem* **21** 730–8

[27] Holshue M L *et al* Washington State-nCo VCI 2020 First case of 2019 novel coronavirus in the United States *N. Engl. J. Med.* **382** 929–36

[28] Ko W C, Rolain J M, Lee N Y, Chen P L, Huang C T and L P I 2020 Arguments in favor of remdesivir for treating SARS-CoV-2 infections *Int. J. Antimicrob. Agents* **55** 105933

[29] Colson P, Rolain J M and Raoult D 2020 Chloroquine for the 2019 novel coronavirus SARS-CoV-2 *Int. J. Antimicrob. Agents* **55** 2

[30] Szucs Z *et al* 2018 Structure-activity relationship studies of lipophilic teicoplanin pseudoaglycon derivatives as new anti-influenza virus agents *Eur. J. Med. Chem.* **157** 1017–30

[31] Balzarini J, Keyaerts E, Vijgen L, Egberink H, De Clercq E, Van Ranst M, Printsevskaya S S, Olsufyeva E N, Solovieva S E and Preobrazhenskaya M N 2006 Inhibition of feline (FIPV) and human (SARS) coronavirus by semisynthetic derivatives of glycopeptide antibiotics *Antiviral Res.* **72** 20–33

[32] Russell C D, Millar J E and B J K 2020 Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury *Lancet* **395** 473–5

[33] Lai C-C, Liu Y H, Wang C-Y, Wang Y-H, Hsueh S-C, Yen M-Y, Wen-Chien K and Hsueh P-R 2020 Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): facts and myths *J. Microbiol.* **53** 404–12

[34] Derebail V K and Falk R J 2020 ANCA-associated vasculitis - refining therapy with plasma exchange and glucocorticoids *N. Engl. J. Med.* **382** 671–3

[35] Shereen M A, Khan S, Kazmi A, Bashir N and Siddique R 2020 COVID-19 infection: origin, transmission, and characteristics of human coronaviruses *J. Adv. Res.* **24** 91–8

[36] Seok H, Jeon J H and Park D W 2020 Antimicrobial therapy and antimicrobial stewardship in sepsis *Infect. Chemother.* **52** 19–30

[37] Pacios O, Blasco L, Bleriot I, Fernandez-Garcia L, Bardanca M G, Ambroa A, Lopez M, Bou G and Tomas M 2020 Strategies to combat multidrug-resistant and persistent infectious diseases *Antibiotics-Basel* **9** 65

[38] Sobotta L, Skupin-Mrugalska P, Piskorz J and Mielcarek J 2019 Porphyrinoid photosensitizers mediated photodynamic inactivation against bacteria *Eur. J. Med. Chem.* **175** 72–106

[39] Sobotta L, Skupin-Mrugalska P, Piskorz J and Mielcarek J 2019 Non-porphyrinoid photosensitizers mediated photodynamic inactivation against bacteria *Dyes Pigm.* **163** 337–55

[40] Mesquita M Q, Dias C J, Neves M, Almeida A and Faustino M A F 2018 Revisiting current photoactive materials for antimicrobial photodynamic therapy *Molecules* **23** 47

[41] Schultz E W and K A P 1928 Inactivation of Staphylococcus bacteriophage by methylene blue *Proc. Soc. Exp. Biol. Med.* **26** 100–1

[42] Felber T D, Smith E B and Jm K 1973 Photodynamic inactivation of herpes simplex: report of a clinical trial *J. Am. Med. Assoc.* **223** 3

[43] Wiehe A, O'Brien J M and Senge M O 2019 Trends and targets in antiviral phototherapy *Photochem. Photobiol. Sci.* **18** 2565–612

[44] Maisch T 2015 Resistance in antimicrobial photodynamic inactivation of bacteria *Photochem. Photobiol. Sci.* **14** 1518–26

[45] Jockusch S, Lee D, Turro N J and Leonard E F 1996 Photo-induced inactivation of viruses: adsorption of

methylene blue, thionine, and thiopyronine on Q beta bacteriophage *Proc. Natl. Acad. Sci. U. S. A.* **93** 7446–51
[46] Wainwright M 2003 Local treatment of viral disease using photodynamic therapy *Int. J. Antimicrob. Agents* **21** 510–20
[47] Girotti A W 1990 Photodynamic lipid-peroxidation in biological-systems *Photochem. Photobiol.* **51** 497–509
[48] Bonnett R 1995 Photosensitizers of the porphyrin and phthalocyanine series for photodynamic therapy *Chem. Soc. Rev.* **24** 19–33
[49] Wainwright M, Maisch T, Nonell S, Plaetzer K, Almeida A, Tegos G P and Hamblin M R 2017 Photoantimicrobials-are we afraid of the light? *Lancet Infect. Dis.* **17** e49–e55
[50] Eduardo C D, Aranha A C C, Simoes A, Bello-Silva M S, Ramalho K M, Esteves-Oliveira M, de Freitas P M, Marotti J and Tuner J 2014 Laser treatment of recurrent herpes labialis: a literature review *Lasers Med. Sci.* **29** 1517–29
[51] Schlenke P 2014 Pathogen inactivation technologies for cellular blood components: an update *Transfus. Med. Hemother.* **41** 309–25
[52] Wallis C and Melnick J L 1963 Photodynamic inactivation of poliovirus *Virology* **21** 332–41
[53] Hamblin M R and Hasan T 2004 Photodynamic therapy: a new antimicrobial approach to infectious disease? *Photochem. Photobiol. Sci.* **3** 436–50
[54] Malik Z, Ladan H and Nitzan Y 1992 Photodynamic inactivation of gram-negative bacteria - problems and possible solutions *J. Photochem. Photobiol.* B **14** 262–6
[55] Calzavara-Pinton P, Rossi M T, Sala R and Venturini M 2012 Photodynamic antifungal chemotherapy *Photochem. Photobiol.* **88** 512–22
[56] Santezi C, Reina B D and Dovigo L N 2018 Curcumin-mediated photodynamic therapy for the treatment of oral infections-A review *Photodiagn. Photodyn. Ther.* **21** 409–15
[57] Cieplik F, Tabenski L, Buchalla W and Maisch T 2014 Antimicrobial photodynamic therapy for inactivation of biofilms formed by oral key pathogens *Front. Microbiol.* **5** 17
[58] Floyd R A, Schneider J E and Dittmer D R 2004 Methylene blue photoinactivation of RNA viruses *Antiviral Res.* **61** 141–51
[59] Moore C, Melnick J L, Wallis C and Kuns M D 1972 Photodynamic treatment of herpes keratitis *Infect. Immun.* **5** 169–71
[60] Kucera L S, Gusdon J P, Edwards I and Herbst G 1977 Oncogenic transformation of rat embryo fibroblasts with photo-inactivated herpes-simplex virus–rapid invitro cloning of transformed-cells *J. Gen. Virol.* **35** 473–85
[61] Mullooly V M, Abramson A L and Shikowitz M J 1990 Dihematoporphyrin ether-induced photosensitivity in laryngeal papilloma patients *Lasers Surg. Med.* **10** 349–56
[62] Boyland E, Gaddum J H and McDonald F F 1947 Nasal filtration of airborne droplets *J. Hyg.* **45** 290–6
[63] Kumar N, Sharma S, Barua S, Tripathi B N and Rouse B T 2018 Virological and immunological outcomes of coinfections *Clin. Microbiol. Rev.* **31** 39
[64] Cassidy C M, Tunney M M, Magee N D, Elborn J S, Bell S, Singh T R R and Donnelly R F 2011 Drug and light delivery strategies for photodynamic antimicrobial chemotherapy (PACT) of pulmonary pathogens: A pilot study *Photodiagn. Photodyn. Ther.* **8** 1–6
[65] Haidaris C G, Foster T H, Waldman D L, Mathes E J, McNamara J and Curran T 2013 Effective photodynamic therapy against microbial populations in human deep tissue abscess aspirates *Lasers Surg. Med.* **45** 509–16
[66] Michutova M, Mrazova V, Kudelova M, Smolinska M, Supolikova M, Vrbova M and Golais F 2017 Herpes simplex viruses type 1 and 2 photoinactivated in the presence of methylene blue transform human and mouse cells in vitro *Acta Virol.* **61** 308–15
[67] Shikowitz M J *et al* 2005 Clinical trial of photodynamic therapy with meso-tetra (hydroxyphenyl) chlorin for respiratory papillomatosis *Arch. Otolaryngol. Head Neck Surg.* **131** 99–105
[68] Zhou C Y, Sun B C, Wang F, Dai Z Y, Han Z L, Han J H, Chen M M and Shen Y 2014 Coblation plus photodynamic therapy (PDT) for the treatment of juvenile onset laryngeal papillomatosis: case reports *World J. Surg. Oncol.* **12** 6
[69] Lieder A, Khan M K and Lippert B M 2014 Photodynamic therapy for recurrent respiratory papillomatosis *Cochrane Database Syst. Rev.* **2014** 6
[70] Zhang Y J, Yang Y G, Zou X B and Huang Z 2016 5-Aminolevulinic acid photodynamic therapy combined with co2 laser therapy in treatment of laryngeal papilloma: case report *Photodiagn. Photodyn. Ther.* **14** 131–3
[71] Blanco K C, Inada N M, Carbinatto F M, Giusti A L and Bagnato V S 2017 Treatment of recurrent pharyngotonsillitis by photodynamic therapy *Photodiagn. Photodyn. Ther.* **18** 138–9
[72] Blanco K C, Giusti A L, Inada N M and Bagnato V S 2017 Curcumin gum: use of photodynamic therapy in children with acute pharyngotonsillitis *Int. J. Curr. Med. Pharm. Res.* **3** 1665–7
[73] Lago A D N, Furtado G S, Ferreira O C, Diniz R S and Goncalves L M 2018 Resolution of herpes simplex in the nose wing region using photodynamic therapy and photobiomodulation *Photodiagn. Photodyn. Ther.* **23** 237–9
[74] Kassab G, Geralde M C, Inada N M, Achiles A E, Guerra V G and Bagnato V S 2019 Nebulization as a tool for photosensitizer delivery to the respiratory tract *J. Biophotonics* **12** e201800189
[75] Geralde M C, Leite I S, Inada N M, Salina A C G, Medeiros A I, Kuebler W M, Kurachi C and Bagnato V S 2017 Pneumonia treatment by photodynamic therapy with extracorporeal illumination - an experimental model *Physiol. Rep.* **5** 7
[76] Costa L, Tome J P C, Neves M, Tome A C, Cavaleiro J A S, Faustino M A F, Cunha A, Gomes N C M and Almeida A 2011 Evaluation of resistance development and viability recovery by a non-enveloped virus after repeated cycles of aPDT *Antiviral Res.* **91** 278–82
[77] Costa L, Faustino M A F, Neves M, Cunha A and Almeida A 2012 Photodynamic inactivation of mammalian viruses and bacteriophages *Viruses-Basel* **4** 1034–74
[78] Hamblin M R and Hasan T 2004 Photodynamic therapy: a new antimicrobial approach to infectious disease? *Photochem. Photobiol. Sci.* **3** 14