

Quantum dots and photodynamic therapy in COVID-19 treatment

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Abstract

Viral diseases are regarded as a global burden. The eradication of viral diseases is always a challenging task in medical research due to the high infectivity and mutation capability of the virus. The ongoing COVID-19 pandemic is still not under control even after several months of the first reported case and global spread. In the pursuit of a promising strategy, carbon dots could be considered as potential nanostructure against this viral pandemic. Carbon dots are photoluminescent carbon nanoparticles, smaller than 10 nm in dimension with a very attractive photostable and biocompatible properties which can be surfaced modified or functionalized. These photoluminescent tiny particles have captured much attention owing to their functionalization property and biocompatibility. Photodynamic therapy (PDT) is a technique that is widely used in cancer treatment and against various microbes. In this technique, a light-induced photosensitizer generates reactive oxygen species (ROS), ultimately killing the target cells. Considering these facts, an attempt has been made to review the current literature on viral inactivation using PDT approach. Accordingly, the mechanism of PDT action has been discussed, along with an update on the use of various photosensitizers (PSs) and nanoparticles. The capsid proteins and nucleic acid (RNA) of SARS-CoV-2 can be a possible target for PDT.

KEYWORDS

quantum dot, photodynamic therapy, photosensitizers

1 | INTRODUCTION

The use of fluorescent nanoparticles as probes for bioanalytical applications is a highly promising technique because fluorescence-based techniques are very sensitive. Quantum dots¹ seem to show the greatest promise as labels for tagging and imaging in biological systems owing to their photostability, which allow long-term observations of biomolecules.² The usage of quantum dots in practical applications is extremely important in order to provide safe and effective biosensing materials for medicine.

Quantum dots are a central topic in nanotechnology. They are semiconductor particles a few nanometers in size, having optical and electronic properties that differ from larger particles due to quantum mechanics.³ When the quantum dots are illuminated by UV light, an electron in the quantum dot can be excited to a state of higher energy. For a semiconducting quantum dot, this process corresponds to the transition of an electron from the valence band to the conduction band.⁴ The excited electron can drop back into the valence band releasing its energy by the emission of light and the color of that light depends on the energy difference between the conduction band and the valence band⁵ as shown in Figure 1.

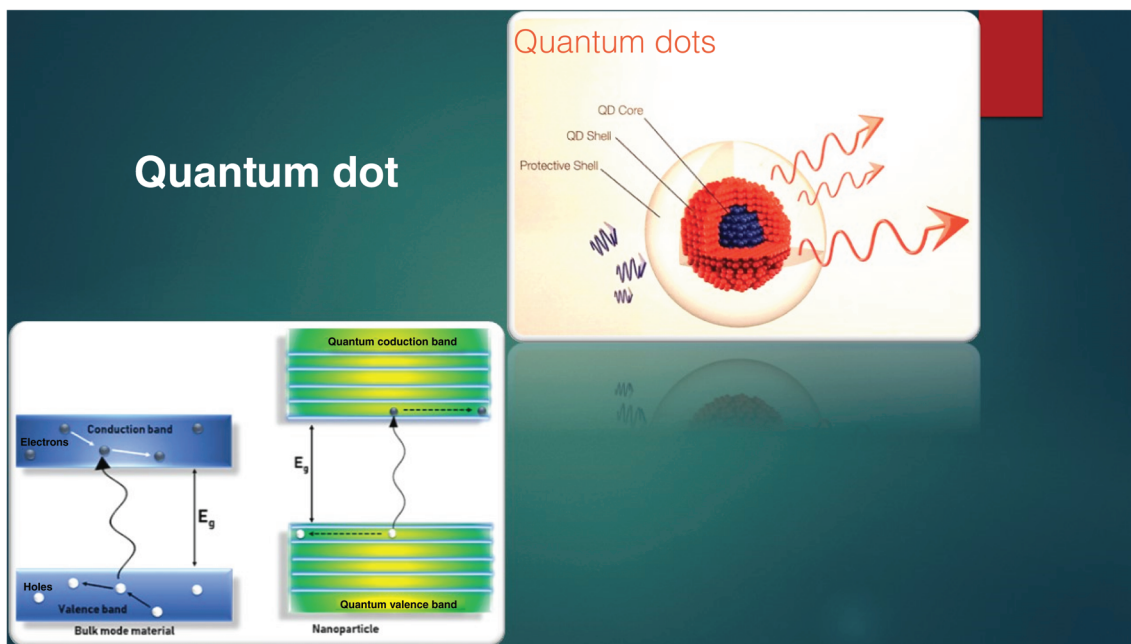


FIGURE 1 Quantum dot—semiconductor particles a few nanometers in size, having optical and electronic properties that differ from larger particles due to quantum mechanics. Here it is shown the transition between valence band and conduction band

Nanoscale semiconductor materials tightly confine either electrons or electron holes. Quantum dots are sometimes referred to as artificial atoms, emphasizing their particularity, having bound, discrete electronic states, like naturally occurring atoms or molecules.⁶ It was shown that the electronic wave functions in quantum dots resemble the ones in real atoms⁷ and that coupling two or more such quantum dots (carbon quantum dots) an artificial molecule can be made, exhibiting hybridization even at room temperature.⁸

Potential applications of quantum dots include single-electron transistors, solar cells, LEDs, lasers, quantum computing,⁹ cell biology research,¹⁰ microscopy,¹¹ and medical imaging.¹²

On March 11, 2020 the World Health Organization (WHO) declared COVID-19 a pandemic, on that day the number of confirmed cases of such disease was over 118,000 and spread over 110 countries, 1 month later that number was close to two million cases and over 200 countries. However, in less developed regions and even many developed countries have suffered, they still suffer from the overload on their health systems. Considering the high cost of existing treatments and medications, it was necessary to seek alternative methods to alleviate this situation and seek to eradicate the virus. With that in mind, we present a way to iterate quantum dots with pathogens that could be threats to health in general. For this purpose, we propose the quantum dots interaction technique associated with photodynamic methodology, which is effective and noninvasive.

2 | QUANTUM DOTS

Quantum dots were theorized in the 1970s as a form of semiconductor nanoparticles and were created from the 1980s onwards. Quantum dots are man-made nanoscale crystals first theorized as nanoparticles of semiconductors in the 1970s and initially produced in the early 1980s. When UV light hits these crystals they can emit light of various colors, and this property has found many applications such as solar cells, fluorescent biological labels, and composite materials.^{13,14} Quantum dots are typically made up of an insulating or semiconductor element, such as carbon (almost always bonded to hydrogen),^{15,16} silicon, germanium, and phosphorus.^{17,18} Despite expressing good optical properties, many of them are toxic to the body because they can contain elements such as cadmium, mercury, zinc, and arsenic.^{19–21}

Recently, carbon quantum dots are attracting attention for having low toxicity properties.^{22–24} Carbon quantum dots are attracting attention for their low toxicity and biocompatibility. They are high hydrophilic, water-soluble, and chemically stable, which are desirable character for many biomedical applications, including drug delivery vehicles.^{25,26}

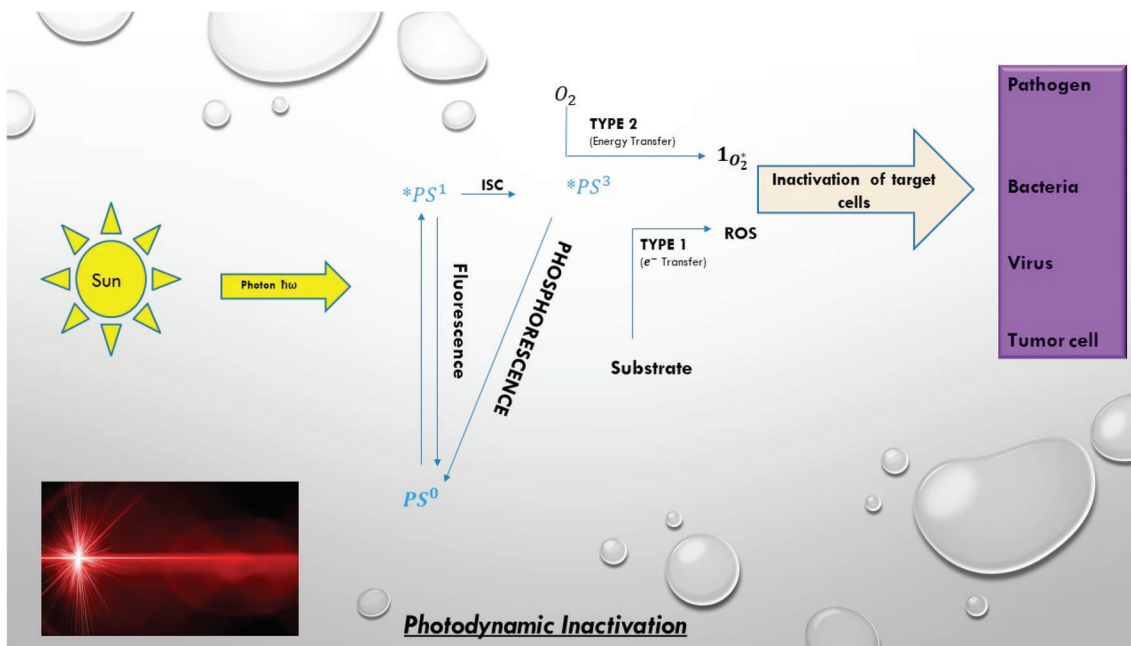


FIGURE 2 Photodynamic methodology—phototherapy involving light and a photosensitizing chemical substance, used in conjunction with molecular oxygen to elicit cell death

3 | PHOTODYNAMIC THERAPY

Several light sources techniques using lasers and LEDs have been increasingly improved for insertion in medical protocols. These applications stem for the fact that they can produce photochemical changes at the cellular level.²⁷ We can cite as treatments that use light, of low intensity or in some cases with high intensity, from skin lesions, treatments for tissue rejuvenation (aesthetics), herpes until recently cases involving malignant cancers of the head, neck, and also related to the skin.^{28–31} Using light as medical treatment has gained notoriety for being minimally invasive, as well as minimally toxic.³² Next, we present the photodynamic therapy technique, also known as PDT, which uses a photosensitizer activated by light of a specific wavelength in the presence of oxygen, and is used as antimicrobial treatment.³³

Photodynamic therapy is based on the principle of using light as an agent associated with photosensitizers (PS) such as aminolevulinic acid (ALA), methyl amino-levulinate (MAL), methylene blue, porphyrin, and curcumin-based molecules.³³ Upon activation, the energy that activates the photosensitizer is transferred to oxygen, causing the release of toxic oxygen species and free radicals (ROS) that completely damage³⁴ cell components of microbial pathogens shown in Figure 2. The preirradiation time—the time required for the photosensitizer to cross the cell membrane barrier—is an important factor on the success of treatment involving PDT. During this period, it does not undergo degradation before achieving this goal. PDT can be one of the complementary or alternative treatments to target SARS-CoV-2. Upon excitation, ROS's major targets formed upon excitation of photosensitizers can target viral membrane, proteins, and RNA of SARS-CoV-2, which could lead to the complete inactivation of the virus.³⁴

4 | SARS-COV-2

Initially spreading only in bat populations, SARS-CoV-2 is not the only variant present in the *Betacoronavirus* family. In previous years other members of this family, such as the SARS-CoV and MERS-CoV were also responsible for epidemic diseases in the Middle East and South East Asia.³⁵

Its structure remembers the shape of a crown whose structures can be classified as saber, nucleocapsid, envelope, and membrane with proteins adhered to its capsule (outer envelope), in which the Spike protein as prominent and hemagglutinin esterase dimerproteins. Inside the virus membrane, there is a single strand of RNA of about 30,000 nucleotides.³⁶

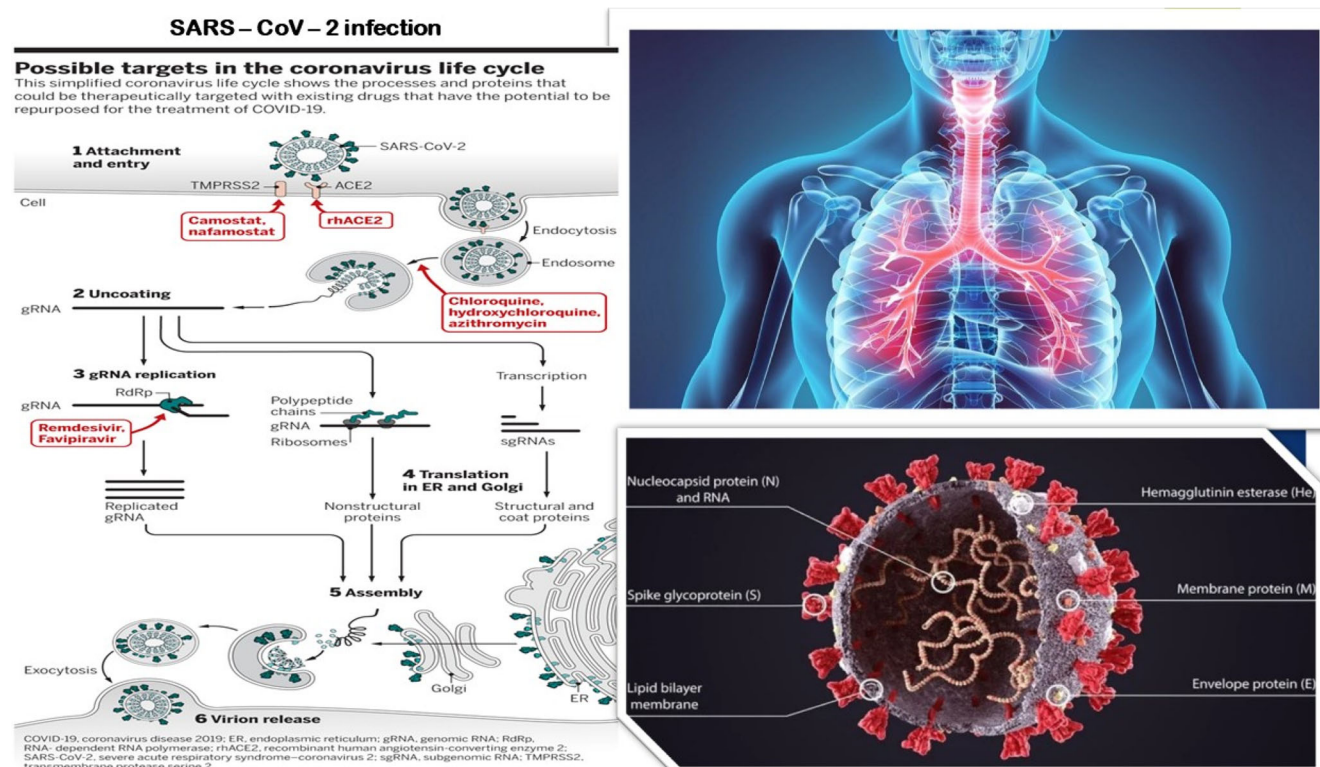


FIGURE 3 SARS-CoV-2–interaction between Spike protein and ACE2 enzyme provokes the trigger for the cycle of SARS-CoV-2 initiate. When the virus is inside the cell, its genetic material contacts with human genetic material in order to replicate

The Spike protein has an important role when the virus tries to infect a host cell. In humans, the Spike protein has an affinity with an enzyme present in healthy cells called angiotensin-converting enzyme2 (ACE2), which is present in the membrane of human cells in the lower respiratory tract of the lungs, stomach, small intestine, colon, kidney, lymph nodes, and hepatic bile ducts.³⁷ By coupling itself to this enzyme via the Spike protein, the virus is able to break the plasma membrane, enter human cells, and expose its genetic material causing severe damage to human RNA and DNA as shown in Figure 3. Because of that, of where most of the cells with ACE2 are located, the virus can cause severe respiratory symptoms.³⁸

Taking into account the high rate of contamination, a way to intensify the results obtained with photodynamic therapy would be to implement photosensitizers with quantum dots. However, such structures are usually highly cytotoxic to human cells due to the fact that they disrupt phases of the cell respiration cycle by altering Ca^+ levels in mitochondria.³⁹ In a recent article, Garg et al.,⁴⁰ described the inhibitory mechanism of human coronaviruses by hetero atom doped carbon dots. The research group also proposes the potential development of triazole-based carbon dots against SARS-CoV-2 infection using a series of bioisosteres.

Carbon dots derived from benzoxazine monomers by hydrothermal reaction was found to be effective against the porcine parvovirus, dengue virus, Zika virus, and Japanese encephalitis virus. Carbon dots were formed as a result of pyrolysis, carbonization, and oxidization of benzoxazine monomers in the presence of aqueous sodium hydroxide (NaOH) in a Teflon coated stainless steel autoclave.⁴¹ These carbon dots were able to bind directly to viral surface proteins and stop the first step of viral attachment to the host cells as shown in Figure 4.

5 | CARBON QUANTUM DOTS

Curcumin cationic carbon dots (CCM-CDs) can efficiently inhibit coronavirus infection. Curcumin carbon dots were synthesized by the hydrothermal reaction of curcumin and citric acid in a Teflon coated autoclave followed by purification with centrifugation and then dialysis. The CCM-CDs were found to inhibit the entrance of virus, production of the negative strand of RNA as well as budding. Suppression of viral replication was found to be due to stimulation in the

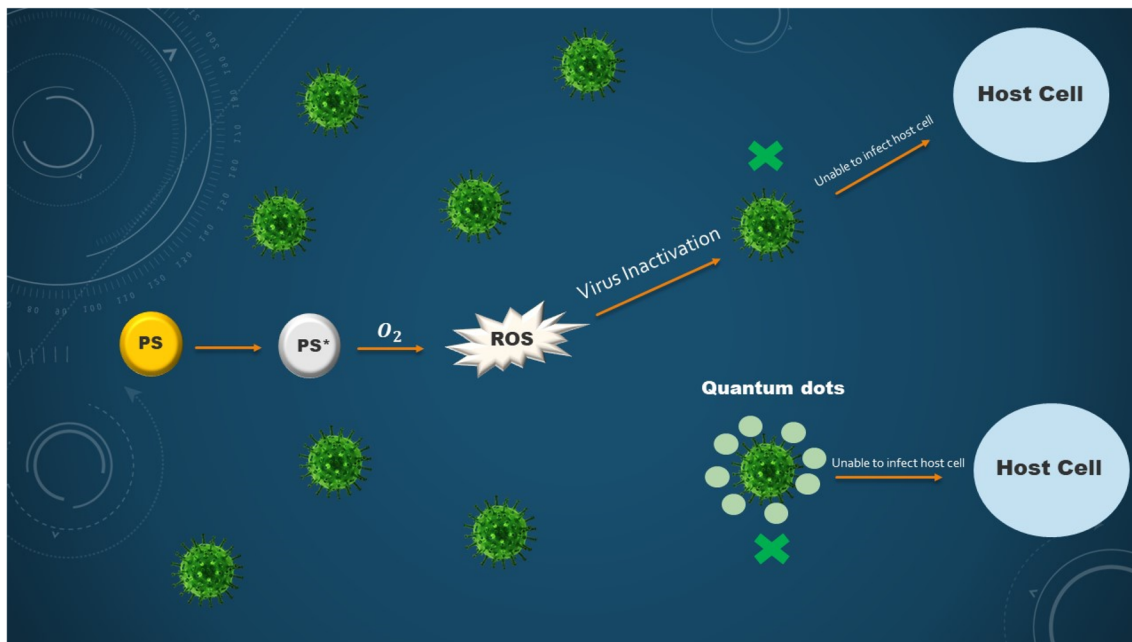


FIGURE 4 Photodynamic therapy mechanism and quantum dots action in order to unable SARS-CoV-2, preserving host cells healthy

production of interferon stimulating genes as well as pro-inflammatory cytokines and also due to the accumulation of ROS. This was proved as a multisite inhibitor for Enteric Coronavirus. This one step ultrasmall sized (1.5 nm) antiviral fluorescent CCM-CDs with a positive charge and many hydrophilic groups obtained by pyrolysis of curcumin are highly effective against coronavirus model (porcine epidemic diarrhea virus).⁴²

Carbon dots can effectively inhibit the replication of RNA viruses like Porcine reproductive and respiratory syndrome viruses. Carbon dots are synthesized by the hydrothermal reaction of PEG-diamine and ascorbic acid in a Teflon coated autoclave chamber. The antiviral activity was tested in vitro on Monkey kidney cells infected with Porcine reproductive and respiratory syndrome viral strain, WUH3. Viral replication is inhibited by increased interferon- α production and enhanced expression of interferon-stimulating genes.⁴³ A broad strategy of anti-coronavirus therapy is not practically possible due to the biodiversity and rapid mutation characteristic of coronaviruses.⁴⁴ Developed seven different types of carbon quantum dots against human coronavirus. The first generation carbon dots were made from ethylenediamine or citric acid by hydrothermal carbonization and then functionalization was carried out by chemical integration of boronic acid. The second-generation carbon dots were prepared from 4-aminophenyl boronic acid. Inhibition of HCoV-229E entry as well as viral replication was achieved with the developed carbon dots.⁴⁴ Boronic acid or amine group surface functionalized carbon dots can inhibit type 1 herpes simplex virus infections. The carbon dots were synthesized from 4-aminophenyl boronic acid hydrochloride by hydrothermal carbonization showed a high potency to prevent the infection in herpes simplex type 1 infected A549 and Vero cells. The research showed that the carbon dots interfere with the entry of the virus into the host cell.⁴⁵

6 | CARBON QUANTUM DOTS AND SARS - COV-2 PHOTODYNAMIC THERAPY

As described in Section 2, the use of quantum dots associated with photodynamic therapy is limited to toxicity factors.⁴⁶ However, carbon quantum dots have promising properties to be used together with PS due to their low toxicity and effectiveness against pathogens. Carbon dots have many advantages over conventional organic PS, such as chemical inertness, high water solubility, photostability, interplay between optoelectronic features and shape and size, good donors in the fluorescence resonance energy transfer process, high stability in physiological conditions, specific accumulation at the target site and facile surface functionalization. These features therefore make carbon dots promising candidates in novel delivery systems for target-specific photosensitization⁴⁷ due to their photoluminescence properties. Considerable efforts

are being made to understand the interplay of features such as size and shape, in concert with the type and quantity of additional functional groups, for the generation of photoluminescence, as well as capacity to act as energy donors for conventional PS.⁴⁸ The energy transfer between carbon dots and cell molecules could potentially induce the generation of ROS, thus provoking cellular apoptosis. The light-mediated cytotoxicity of carbon dots, together with their energy-donor capacity, could therefore open a new area for research in the life sciences, as direct components of conventional photosensitizing agents used in PDT. The ROS production from carbon dots could potentially allow precise therapeutic dosing and therefore, by implementing the PDT technique within carbon dots, can produce more effective results against pathogens as SARS-CoV-2.

7 | CONCLUSION

Photodynamic therapy has been used for the treatment of cancer cells, inactivation of pathogens, including viruses. Despite this, PDT process is gaining popularity just recently. The search for alternative therapeutic approaches for the effective management of COVID-19 has been made to introduce the possibility of exploring PDT as an alternative or complementary treatment for COVID-19. The PS and light play an important role in this process. With the advances in technology, nanoparticles can also be used for increasing the therapeutic efficacy of the PDT treatment. This review offers an updated discourse on PSs and nanoparticles used in PDT process along with mechanisms underlying PDT mediated inactivation of tumor cells, pathogens, viruses.

Carbon dots have proved promising application against different types of corona viruses. Still, more focus required to be given in exploring carbon dot-based antiviral agents for treating SARS-CoV, MERS-CoV, and SARS-CoV-2 viral infections. Carbon dots are extensively researched in biomedicine other than therapy like biosensing, bioimaging, and so forth. Surface functionalization and low toxicity makes carbon dots the most superior among other nanoparticulate therapeutic delivery systems. These functionalized carbon dots can stay as a new stage for the production of biosafe nanotherapeutics for treating viral infections in the near future. Among the reviewed researches carbon dots derived from herbal sources like curcumin, glycyrrhizin, and so forth was found to be more promising because of their biocompatibility, lower toxicity, and strong in vitro as well as in vivo antiviral activity.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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