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Nip in the bud: can carbon/quantum dots be a prospective nano-theranostics against COVID-19?

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Abstract. COVID-19 inflicted by the SARS-CoV-2 virus has created mayhem across the globe and has afflicted socio-economic, political and cultural aspects of every nook of the world. Notwithstanding, the ensuing COVID-19 waves are still approaching and squeezing the economies of developed and developing worlds. Nanobiotechnology-driven interventions in COVID-19 may facilitate nipping in the bud at an early stage, consequently managing the menace of the virus. Nanostructures, notably luminescent carbon/quantum dots (C/QD), are potential nanomedicines in the field of theranostics and pharmaceuticals. They have stood the test of time due to their ease of synthesis, minimal toxicity, significant biocompatibility, tunable fluorescence, surface tenability, excellent photochemical stability and good hydrophilicity. In this mini-review, we have considered the recent findings of C/QD as potential nano-theranostics against COVID-19. Furthermore, we have also discussed antiviral modes of different C/QD. This mini-review will provide brief oversight and offer a new strategy to develop C/QD-based antiviral agents for future-ready pandemics.

Keywords. SARS-CoV-2 virus; nanosensors; nanomaterials; luminescence; carbon/quantum dots; nano-theranostics.

1. Introduction

COVID-19 is one of the most dreadful pandemics that caused a havoc to the human population irrespective of caste, societal status, creed, sex or religion. Until August 2023, the World Health Organization (WHO) has reported more than 765 million confirmed cases of COVID-19 and more than 6.9 million deaths across the globe. Therefore, timely diagnosis and treatment of COVID-19 is a vital step in curbing the further dissemination of the virus across the world [1].

Along with India, the rural populations of other developing countries have been significantly shattered by the recent waves. It is not only that this pandemic has hit humans, but also other living beings have been gravely affected. Hence the notion of 'One World One Health' is the need of the hour. As we say, every dark cloud has a silver lining, and COVID-19 is no exception to this. This pandemic has exemplified the silver lining of innovative approaches for developing diagnostic kits for COVID-19, innovative vaccines, the emergence of digital education, digital health missions, etc.

COVID-19 fomented by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has become one of the most dreaded infectious diseases that has hardly left any part of the globe untouched. For the last few decades, the vaccination development program would take approximately 10–12 years, but with advances in nanobiotechnology and virology, several vaccines have been launched with Emergency Use Authorization (EUA) from competent authorities within 1 year. This pandemic has necessitated a more rapid and accurate diagnosis than ever before. Apart from reverse transcription polymerase chain reaction (RT-PCR) for the RNA of SARS-CoV-2, which is considered to be a gold standard diagnostic method for its detection, as available now, other methods such as loop-mediated isothermal amplification (LAMP) processes are also clinical use [2]. World Health Organization has approved Moderna, Janssen, Pfizer-BioNtech, AstraZeneca, Sinopharm, Covishield, etc., to curtail the COVID-19 spread. Apart from that, there are many other vaccines that are still under the

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pipeline. However, due to recurrent mutations and increasing transmissibility, vaccines were not that successful in curbing the spread of the virus.

Carbon-based nanomaterials exhibit remarkable physicochemical properties, including mechanical strength, optical and thermal stability, good biocompatibility and non-toxicity. Owing to its ultra-sensitive attributes of surface area and ionic-electrical mobility, the 2D hexagonally arranged carbon nanomaterials have opened new avenues in the nanobiomedicine field. Carbon-based nanomaterials, especially luminescent carbon/quantum dots (C/QDs), are potential nanostructures in the field of pharmaceuticals and nanobiomedicines. Due to their ease of synthesis, minimal toxicity, significant biocompatibility, tunable fluorescence, surface tenability, excellent photochemical stability, good hydrophilicity, etc., C/QDs have stood the test of time in terms of accuracy and precision. The applications of C/QDs are not merely limited to the health-care operations like biosensing and bioimaging, drug delivery, but also to other domains [3–5], etc. In 2004, Xu *et al* [6] discovered these fluorescent C/QDs for the first time during the purification of single-walled carbon nanotubes. In earlier studies, natural product-derived C/QDs have also revealed promising results in cancer biology [3–5]. Other carbon-based nanomaterials, such as carbon nanotubes, graphene derivatives, fullerenes, etc., have shown wonderful therapeutic attributes in the field of cancer biology apart from anti-infective therapeutics. Due to large surface functional groups, multiple therapeutic moieties can be conjugated into them and thereby augmenting their bioactivities to several folds. Concerning the viral infection cycle, C/QDs treatment might restrain the viral entry into the host [7].

The choice of synthesis processes and precursors used in carbon dot formation have a wide range of effects on the physicochemical and biological aspects of the SARS-CoV-2 virus. The modulation of photoluminescence and the association between C/QD and SARS-CoV-2 virus are influenced by precursor molecules for instance natural antiviral products such as glycyrrhizic acid, Curcumin, and so on. Distinct functional groups on the surface of C/QD, like COOH, OH, NH_2, C=C and so on, can interact effectively with diverse SARS-CoV-2 virus receptors. Reaction duration, synthesis temperature, solvent system, pH of the solution, and other factors influence the amount of carbonization, graphitization and polycondensation during the fabrication of C/QD, which can have a protracted impact on C/QD's interaction with SARS-CoV-2 virus [8–10]. Antiviral activity can be augmented even more through post-synthesis modifications with antiviral compounds. Apparent changes in the molecular state caused by changing the precursors and solvent systems can alter the biological and photoluminescence properties as well [11]. The biochemical interaction and electrical structure can be regulated by the doping strategy [12].

2. SARS-CoV-2 biology

COVID-19, perhaps instigated by the bats, is induced by the virus belonging to the genus *Betacoronavirus* [13]. It brings about severe respiratory disease in humans whose structure comprises a single-stranded positive-sense RNA with approximately 30,000 nucleotides. As shown in figure 1, it owns five structural proteins that are (i) envelope (E), (ii) membrane (M), (iii) nucleocapsid (N), (iv) hemagglutinin esterase dimer proteins (HE) and (v) spike (S) protein [14]. Figure 1a depicts the structure of the SARS-CoV-2 virus. Spike protein has a crucial role in infected cells as it has a significant affinity towards the angiotensin-converting enzyme 2 (ACE2) receptor protein of the host cells. Since ACE2 is an enzyme associated with the cell membranes of the small intestines, colon, lungs, stomach, kidney, liver bile ducts and lymph nodes, it acts as a significant entry point of SARS-CoV-2 [15,16]. At the same time, 16–17 non-structural proteins (ns1 to ns17), such as papain-like protease (PLpro), helicase, RNA-dependent RNA polymerase (RdRp) and 3-chymotrypsin-like protease (3CLpro), are encoded by the SARS-CoV-2 genome. SARS-CoV-2 virus's morphological size was determined using a transmission electron microscope and was found to be in the nanoscale range of 60–140 nm with a 100 nm average. Hence, considering it a nanomaterial, nanotechnology-driven interventions could prove beneficial in developing nano-theranostics against managing the havoc created by the SARS-CoV-2 virus [17]. Prasad *et al* [14] have reported transmission electron microscopy imaging of COVID-19 as depicted in figure 1b [14]. Similarity and differences of SARS-CoV-2 with other deadly viruses are provided in supplementary table S1.

3. Different antiviral mechanisms of C/QDs

Size tenability, traceability under specific wavelength, and penetrability of C/QDs into viruses make them suitable candidates for mitigating the menace of the virus [18]. C/QD can be configurable in size (1–10 nm) and shape to efficiently target SARS-CoV-2, which has a size range of 60–140 nm. Interestingly, the positive surface charges of C/QDs could play a decisive role in the inactivation of S protein by interacting with the virus's negative RNA strand, thereby leading to the generation of reactive oxygen species (ROSs) in the virus [18,19]. C/QD was tested for its ability to prevent negative-strand RNA synthesis. At various hours after infection, the level of virus negative-strand RNA in C/QD-treated cells was much lower than in untreated control cells, implying that C/QD can effectively limit virus replication [20]. The positively charged C/QD on the surface forms strong electrostatic contacts with viral or cell membranes, resulting in a competition for virus-cell binding. Through electrostatic association, positively charged C/QD may cause virus aggregation, resulting in

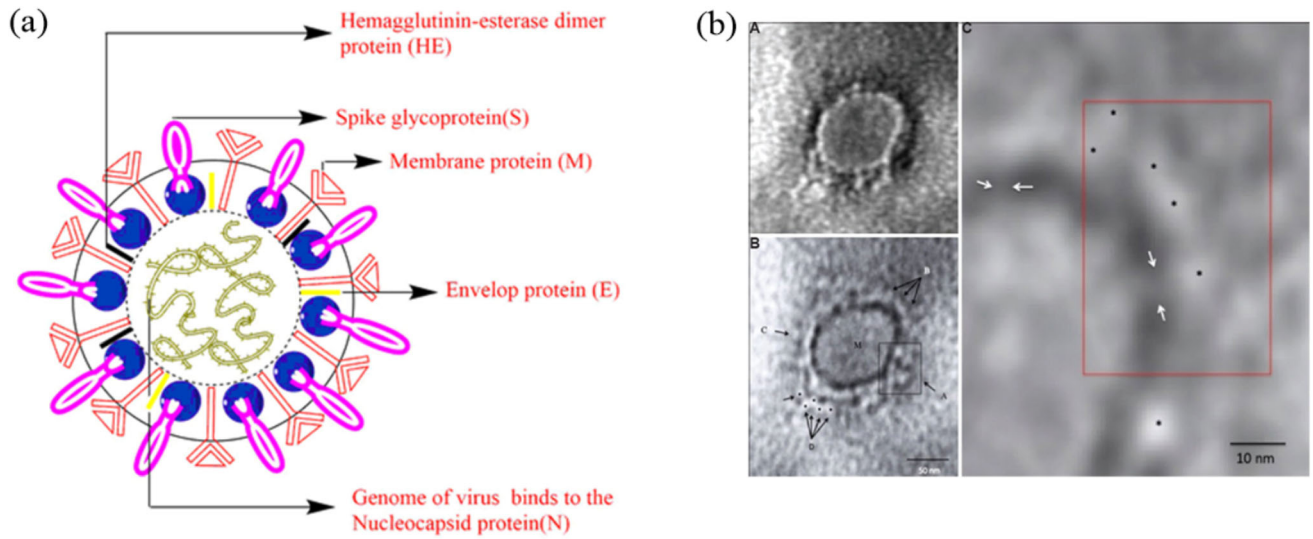

Figure 1. (**a**) Structure of SARS-CoV-2. (**b**) Transmission electron microscopy imaging of SARS-CoV-2.

decreased viral pathogenicity. Certain viruses cause overexpression of reactive oxygen species (ROS), which causes DNA damage through controlling apoptotic signaling pathways. C/QD treatment inhibits viral penetration by modifying the structure of the viral surface protein and limiting the synthesis and budding of negative-strand RNA in the virus [18, 19]. C/QDs intrude with viral replication through different mechanisms. The critical steps involved in viral infection are attachment, penetration, replication, and finally, budding.

Virus entry into the host cells is the primary initiation step of infection. Consequently, blocking this step would lead to the inactivation of the virus. Most reported C/QDs alter the viral surface proteins and thus can interfere in the early stages of viral infections [21]. Altering the cell surface membrane and cell surface proteins can disrupt cell physiology. Electrostatic interaction of positively charged C/QDs led to viral aggregation and inactivation, confirmed through fluorescence analysis and Raman spectral analysis [20]. This study revealed that curcumin-derived C/QDs could effectively hinder viral entry by altering the viral surface protein's structure and preventing viral RNA synthesis and budding. Figure 2 illustrates some essential antiviral mechanisms of C/QDs.

Inhibiting the replication and preventing their budding becomes a substantial approach once the virus enters the body, and this may be achieved by altering the enzymes involved in the viral genome replication. The progeny will bud off as a new virus from the host cells after replication (figure 3a). Curcumin-derived C/QDs are reported to inhibit the production of ROSs induced by coronavirus infections [20]. Du *et al* [22] reported synthesizing C/QDs from PEG-diamine and ascorbic acid via a hydrothermal method by heating at 180°C for 1 h. These C/QDs stimulated the expression of IFN-stimulating genes and the production of interferon-α (IFN-α), which subsequently restrained virus replication [22]. The innate immune system is the first blockade to tackle invasive microorganisms. Type I interferons such as IFN-α and IFN-β are potent innate immune antiviral molecules [23]. Interferon-gamma (IFN-γ) is a cytokine that plays a significant role in innate and adaptive immunity, activating macrophages and boosting natural killer cells and neutrophils [24]. As a result, the immune system's optimal functioning depends on a careful balance between innate and adaptive immunity [25–27]. Another drawback of such methods is the potential for hypersensitivity to develop. The method through which C/QD modulates the immune system is still unknown. A more thorough investigation is warranted, as well as the development of appropriate testing guidelines for the immunological evaluation of C/QD. Aside from viruses, such a method may impact bacteria, including 'good' bacteria. In cell culture, these techniques appear to be effective, but they might have negative consequences *in-vivo*.

Lin *et al* [28] synthesized C/QDs by directly pyrolysing curcumin (figure 3b), and their product yields post-dialysis were recorded in the range of approximately 10–25%. The plaque reduction assay was utilized to confirm the antiviral activities of these C/QDs. Plaque assays are a type of infectivity assay to determine the number of infectious and viable parasites in the given sample and are suitable for evaluating stable transfection efficiency [26,27]. The antiviral effects of these C/QDs were predominantly because of the inhibition of viral attachment, instigation of intracellular signaling cascades, and antioxidant effects. C/QDs also inhibited EV71-induced eIF4G cleavage and the translation of EV71, further reducing phosphorylated p38 kinase expression [28].

Dong *et al* [29] synthesized C/QDs with surface passivation molecules such as 3-ethoxypropylamine and 2′-(ethylenedioxy)bis(ethylamine). The antiviral effects of these C/QDs were due to inhibition of VLPs' binding to

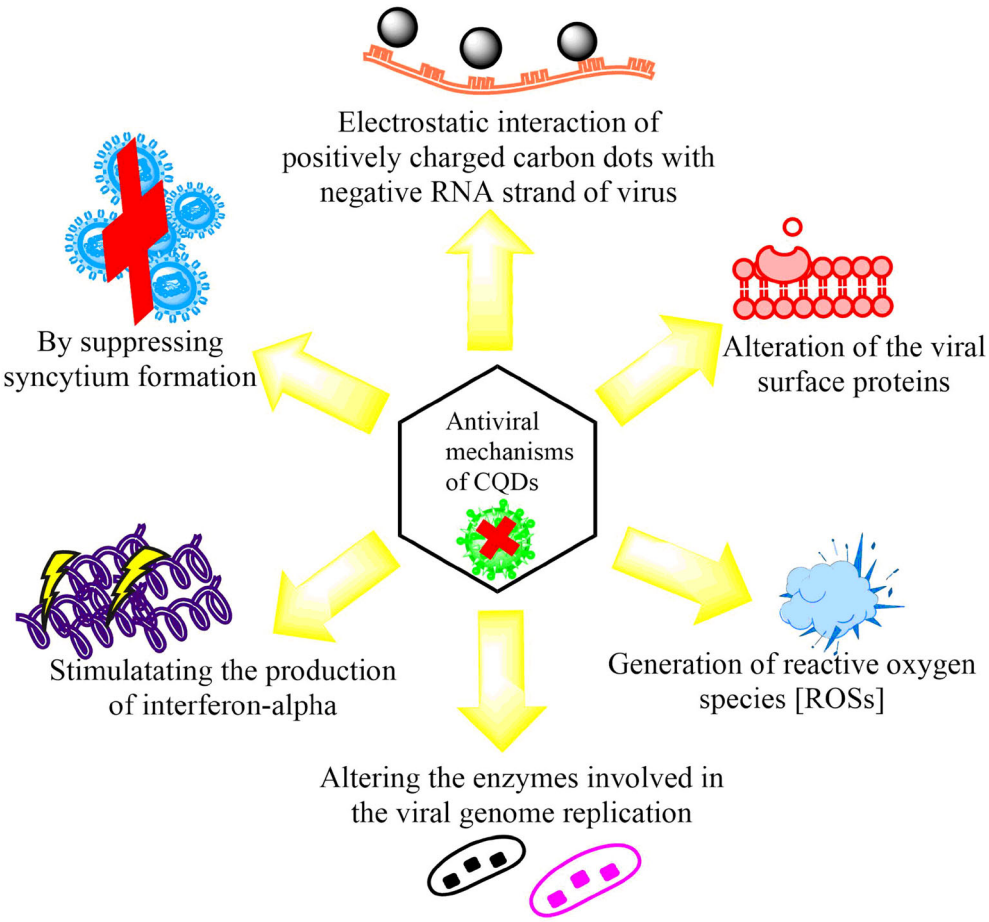

Figure 2. Some of the antiviral mechanisms of carbon/quantum dots (CQDs).

HPGA receptors and inhibition of VLPs' binding to their antibodies [29]. Conversely, Du *et al* [30] fabricated glutathione (GSH) capped CdTe C/QDs, which inhibited virus multiplication. This mechanism is not derived from cytotoxicity; instead, it was due to the interaction between the virus and CdTe C/QDs. These C/QDs change the viral surface protein's structure when adsorbed on the virus surface, leading to the release of Cd^{2+} [30]. Hu *et al* [31] reported that C/QDs induced inhibition of NF-κB prevented viral replication. Fahmi *et al* [32] prepared C/QDs via calcinations of citric acid at 250°C for 30 min, and they were further conjugated with boronic acid-containing molecules (figure 3c). These C/QDs were capable of binding to gp120 protein on the virus and thereby blocking the infection. The presence of boronic acid moieties on the surface of C/QDs augmented the virus inhibition via suppressing syncytium formation [32]. Synctia is formed due to the fusion of infected cells with neighbouring cells, which results in multi-nucleate enlarged cells. The expression of spike protein without any other viral proteins initiates syncytia formation [33,34]. However, not enough studies are available based on animal models to establish the exact mode of antiviral action of C/QDs. In-depth studies might unravel the multi-dimensional aspects of suppressing or inhibiting the virus's growth, especially the SARS-CoV-2 virus.

Duan *et al* [35] reported the anti-PRRSV (porcine reproductive and respiratory syndrome virus) activity of glycyrrhizic acid (GA), with the inhibitory effect of GA at 400 μM (0.33 mg ml^{-1}) and were ≈two orders of magnitude [35]. However, in another study, glycyrrhizic acid-derived C/QDs inhibited PRRSV proliferation with the inhibitory effect of 0.30 mg ml^{-1} with ≈five orders of magnitude. These results indicate that glycyrrhizic acid-derived C/QDs possess enhanced antiviral activity compared to glycyrrhizic acid. Glycyrrhizic acid-derived C/QDs were structurally analogous to glycyrrhizic acid, with functional groups maintained while fabricating C/QDs. However, C/QDs have a large surface area, resulting in polyvalent interactions with the virus [7]. The synthetic conditions such as type of reaction method, reaction duration and temperature influence the morphology and functional groups of C/QDs, which may further exhibit differential antiviral effects in natural products-derived C/QDs [36,37]. The hydrothermal reaction source, temperature and time significantly affect the size and functional groups of as-prepared C/QDs, which could further affect their antiviral activities.

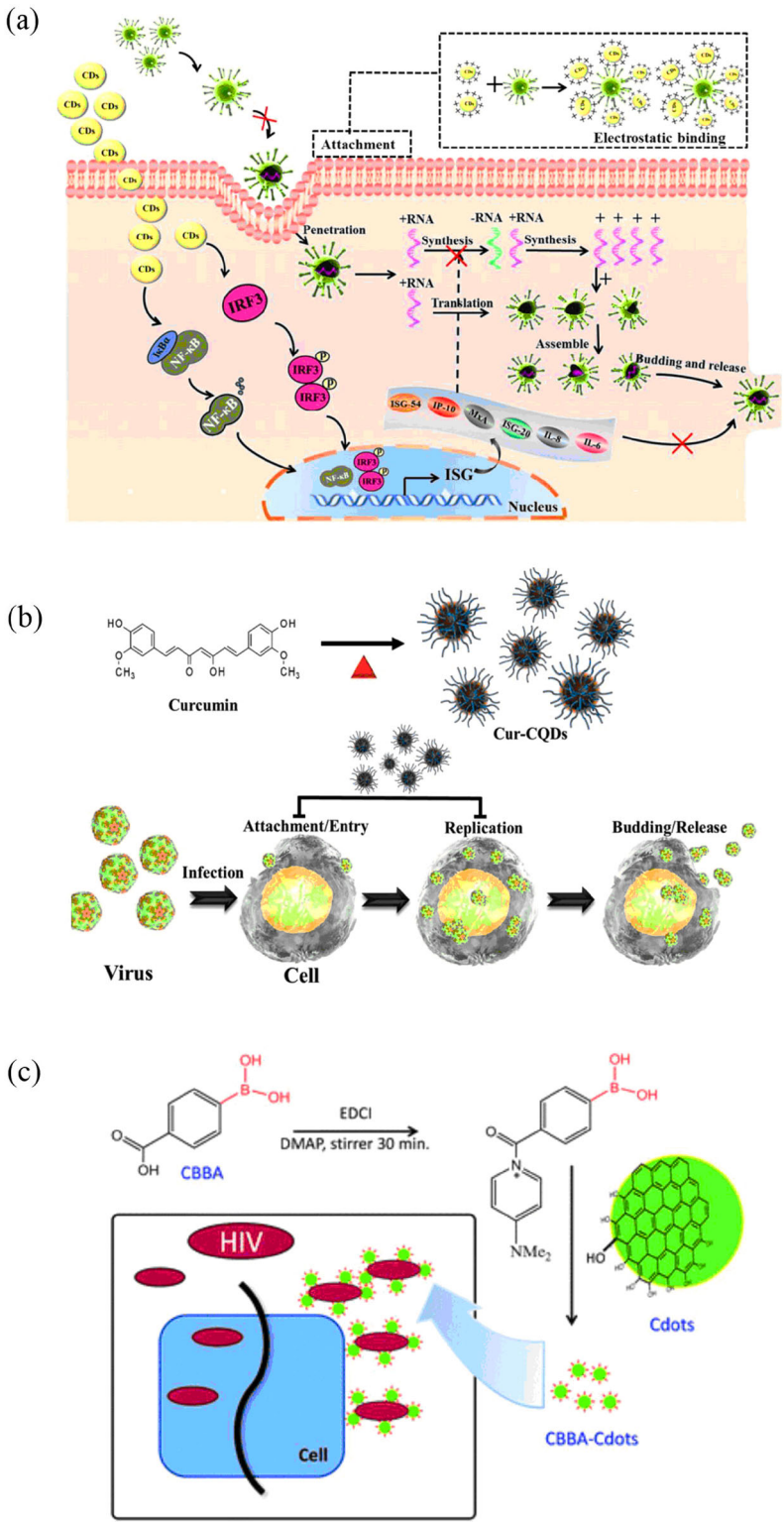

Figure 3. (**a**) Curcumin-based carbon dots with antiviral activity at multiple points in the life cycle of the enteric coronavirus. Reprinted with permission from Ting *et al* [20], Copyright (2018) ACS. (**b**) One-step synthesis of curcumin-derived carbon dots and their antiviral applications. Reprinted with permission from Lin *et al* [28], Copyright (2019) Wiley and Sons. (**c**) Schematic of conjugating CBBA onto carbon dots and other mechanisms on inhibition entry. Reprinted with permission from Fahmi *et al* [32], Copyright (2016) RSC.

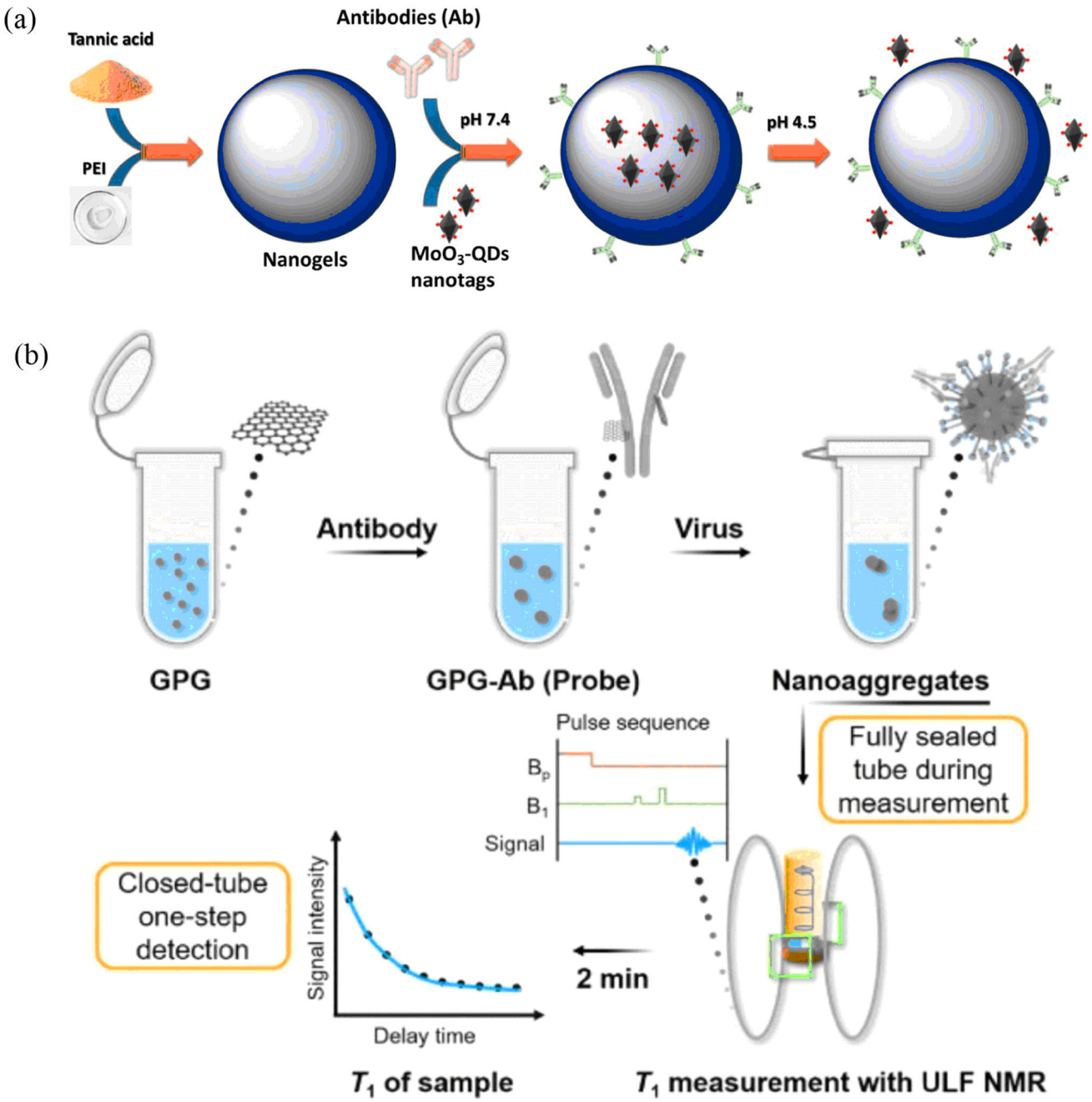

Figure 4. (**a**) MoO_3-QD-based nanotag synthesis and dual functionalization of magnetic NPs to derive Ab-Maleimide-CmagNPs[aq] "Hotspot" formation route by nanotags (via thiol-maleimide affinity interaction). Reprinted with permission from Achadu *et al* [43], Copyright ACS 2021. (**b**) The detection process of the MRSw assay with ULF NMR. Reprinted with permission from Li *et al* [46], Copyright Elsevier 2021.

4. C/QDs as a detection probe for COVID-19

The low concentration of viral load in the samples makes their detection exigent. Hence, the utility of C/QDs as a diagnostic agent is determined based on their accuracy and easy and rapid traceability at specific wavelengths [38]. Photoinduced charge transfer, resonance energy transfer, electron transfer and inner filter property are essential mechanisms for modulating fluorescence properties indispensable for sensing applications [39]. C/QDs exhibit intrinsic fluorescence ability, which promotes their use as an imaging probe in understanding the structures and lifecycle of various pathogens, including viruses. C/QDs have also been reported for bacterial, fungal and yeast bioimaging [40,41]. To summarize, the sensing potential of C/QDs is owed to changes in their fluorescence properties.

Later, Martínez-Periñán *et al* [42] reported an electrochemical biosensor based on the combination of

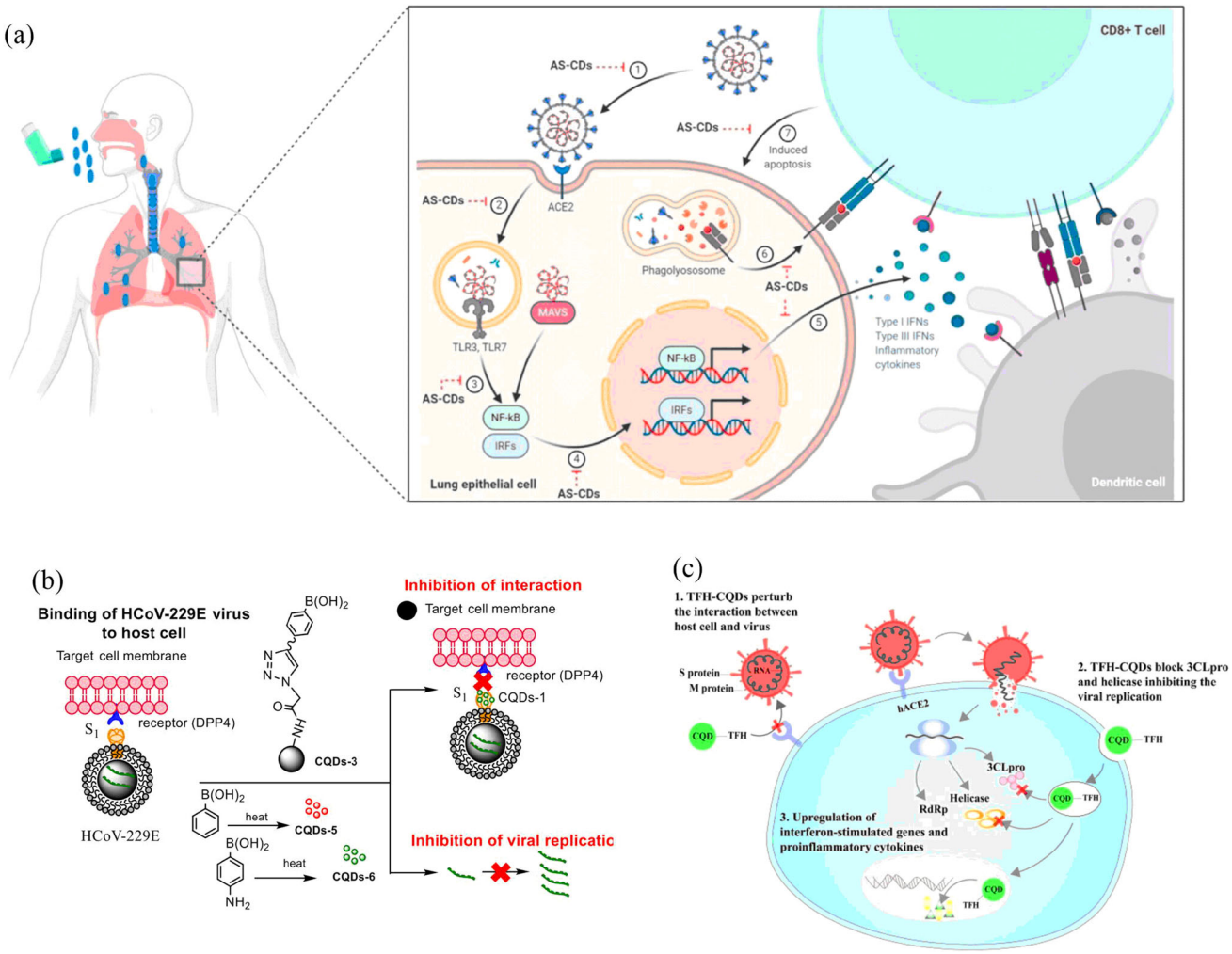

Figure 5. (**a**) This mechanistic figure illustrates different steps where AS-CDs might produce theranostic activity. 1. Entry of coronavirus into the cell through binding ACE2 receptor. 2. Coronavirus initiates a replication cycle inside the host cell. 3. Triggers the cytokine regulatory proteins (NF-κB, IRFs). 4. Induced protein incites the production of inflammatory cytokines. 5. Release of inflammatory cytokines. 6. Degradation of the cellular receptor. 7. Induction of cell apoptosis. Reprinted with permission from Kalkal *et al* [47], Copyright Elsevier 2021. (**b**) Influence of C/QDs, prepared by hydrothermal carbonization, on the binding of HCoV-229E virus to cells: inhibition of protein-S receptor interaction and inhibition of viral RNA genome replication. Reprinted with permission from Łoczechin *et al* [50], Copyright ACS 2019. (**c**) Proposed mechanism of action of TFH-CQDs against SARS-CoV-2. Reprinted with permission from Garg *et al* [49], Copyright Elsevier 2020.

functionalized carbon nanodots and molybdenum disulphide (MoS_2) for sensitive and selective detection of SARS-CoV-2 virus apart from *Listeria monocytogenes*. It is based on the interface between single-stranded oligonucleotide (Probe-SH) and MoS_2 flakes deposited on carbon screen-printed electrodes combined with thionine-functionalized carbon nanodots. Compared to the PCR technique, C/QD fabrication and testing protocols are straightforward, inexpensive and rapid.

In another study, Achadu *et al* [43] reported encapsulation of SERS (surface-enhanced Raman scattering) nanotags containing plasmonic molybdenum trioxide quantum dots (MoO_3-QDs) by pH-responsive nanogels to detect a virus (figure 4a). The pH-induced release of the encapsulated nanotags was due to engineered localized SERS hotspot regions driven by nanotag–maleimide binding affinity. This strategy owed the biosensing platform for the ultrasensitive immunoassays of the virus [43]. C/QDs can be harnessed as a sensing probe depending on the differential rate of adsorption on the C/QD's surface by single and double-stranded DNA [44]. Fabiani *et al* [45] reported the development of a rapid saliva-based electrochemical immunoassay for the detection of SARS-CoV-2 coronavirus. This assay helped detect nucleocapsid/spike proteins in which magnetic beads were used to support the immunological chain and secondary antibody with alkaline phosphatase as the immunological label. In another recent study, Li *et al* [46] reported SARS-CoV-2 detection by magnetic graphene quantum dots using a portable ultra-low field NMR system (figure 4b). This probe can detect a

pseudovirus concentration of as low as 248 particles ml^{-1} within 2 min [46]. Thus, the development of such innovative and cost-effective probes opens avenues for the way to advanced biosensors for the SARS-CoV-2 virus.

5. Carbon/quantum dots as therapeutics against COVID-19

All virus changes over time. Some of these changes may affect the transmissibility and spread of the virus, the performance of vaccines and diagnostic platforms. Due to mutations within SARS-CoV-2, there has been the emergence of various variants of concern such as Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), posing more threat due to its enhanced virulence and transmissibility.

Recently, Kalkal *et al* [47] have reported *Allium sativum*-derived C/QDs as a promising theranostic agent with antiviral and bioimaging potential for COVID-19 (figure 5a). *Allium sativum* is a traditional medicinal herb that exhibits anti-inflammatory potential by limiting the activation of nuclear factor-kappa B [48]. Hence, the C/QDs derived from *Allium sativum* might play an indispensable role in downregulating the expression of pro-inflammatory cytokines and improving the immunological anomalies of COVID-19 [47]. Heteroatom doping, surface passivation and defect formation modulate C/QDs' physicochemical properties to a greater extent. This affects the virus–host cell interactions at multifold levels [49]. Łoczechin *et al* studied the antiviral activity of two different generations of C/QDs to manage human coronavirus HCoV-229E infections (figure 5b). The antiviral action of these C/QDs was due to the inhibition of HCoV-229E entry. This was due to the interaction between cell surface proteins and functional groups of C/QDs. They also influence the virus's genomic replication [50]. Garg *et al* [49] fabricated C/QDs derived from *p*-phenylenediamine, borax and citric acid (figure 5c). They examined the antiviral role of triazole-functionalized heteroatom co-doped C/QDs (TFH-C/QDs) towards human coronavirus. These C/QDs may block the viral enzymes necessary for viral replication, such as 3CLpro and helicase, or block the viral entry [49].

6. Conclusion

All viruses change over time. Some of these changes may affect the transmissibility and spread of the virus, the performance of vaccines, diagnostic platforms and therapeutic platforms. Since coronaviruses are diverse and rapidly mutating at a more incredible pace, anticoronavirus therapy is cumbersome and complex. So it is the need of the hour to look for novel nano-technology-based interventions for timely restricting the occurrences of virus pandemics. However, not enough studies are available based on *in-vivo* animal models to establish the exact mode of antiviral action of C/QD. In-depth studies might unravel the multi-dimensional aspects of suppressing or inhibiting the virus's growth, especially the SARS-CoV-2 virus. Evidence of C/QD's antiviral efficacy is mostly based primarily on *in-vitro* models. To switch to *in-vivo* models, C/QD must not only be non-toxic and efficacious in regulating viral infection but also hydrophilic and colloidally stable under physiological settings. It should be emphasized that robust *in-vivo* models of viral infections are harder to achieve; therefore, assessing the antiviral effectiveness of C/QD *in-vivo* remains a challenging task. Because the mechanisms of action primarily involve preventing the viral particle's contact with the target cell, the most significant antiviral effect is seen during the early stages of infection. As a result, C/QD's usefulness at advanced stages of infection may be limited. Moreover, to get towards practical health applications, present findings must be backed up by substantial *in-vivo* research, which is currently lacking. Natural products-derived eco-friendly C/QD can be employed successfully to augment the antiviral activities of pristine natural products and to overcome the limitations of current viral theranostics agents. Having glanced at the literature available, more toxicological and pharmacodynamics studies of C/QD in appropriate animal models will definitely reveal new dimensions to antiviral research. Last but not least, nanotechnology-driven interventions will be an efficacious strategy in accomplishing the Sustainable Development Goals 3, i.e., Good health and well-being amidst this COVID-19 pandemic [51,52].

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