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Carbon and Graphene Quantum Dots as Bionanomaterials: A Perspective View of COVID–19

Mohd Hayrie Mohd Hatta[a],*, Kalaivani Batumalaie[b], Juan Matmin[c], Johnathan Malagobadan[d]

[a] Centre for Research and Development, Asia Metropolitan University, 81750 Johor Bahru, Johor, Malaysia
[b] Department of Biomedical Sciences, Faculty of Health Sciences, Asia Metropolitan University, 81750 Johor Bahru, Johor, Malaysia
[c] Department of Chemistry, Faculty of Science, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia
[d] Faculty of Medicine, University of Cyberjaya, 63000 Cyberjaya, Selangor, Malaysia

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*Corresponding author
hayrie@amu.edu.my

Abstract

The rapid outbreak of the deadly and contagious SARS-CoV-2 virus in 2019 that caused COVID-19 disease has demanded the development of novel antiviral materials. Since medical treatment and drug evaluation and approval by health authorities takes a longer time, nanomaterials can play a significant role in combating deadly disease. Carbon-based materials, such as carbon nanotubes (CNTs), graphene, fullerene, and carbon quantum dots (CQDs), have been widely reported in the literature as contributing to fighting the viral disease. Among them, CQDs have received significant attention as bionanomaterials recently, particularly in the biomedical field to treat various viral infections. Therefore, this mini-review discusses the recent achievements of CQDs and graphene quantum dots (GQDs) as bionanomaterials in fighting viral disease, specifically COVID-19 and other COVID-19-related works such as sensing and treatment, as well as virus inhibition.

Keywords Carbon quantum dots, graphene quantum dots, SARS-CoV-2, sensor, treatment

1.0 INTRODUCTION

Since December 2019, we have been experiencing a pandemic caused by the SARS-CoV-2 virus which causes COVID-19. This pandemic has affected many people around the world and has caused many deaths (Ting et al., 2023). Within that period, various prevention, detection, and treatment strategies have been reported and are currently being used to prevent the transmission chain of the disease (Hatta et al., 2023). In April 2022, the Malaysian government announced the transition from pandemic to endemic after 95% of Malaysian adults were fully vaccinated. Additionally, 70% of the world population had received at least one dose of the vaccine. (Syafiqah Salim, The Edge). Although most countries in the world are recovering from this public health crisis, the virus remains a major threat to the world (Adam, 2023). For example, China recently reported a daily of *ca*. 13,000 COVID-19 cases in early January 2023 (Li et al., 2023). Therefore, the development of antiviral tools or materials to completely combat this deadly and highly contagious virus is urgently needed.

Carbon-based materials such as carbon nanotubes (CNTs) and graphene, as well as carbon quantum dots/graphene quantum dots (CQDs/GQDs), have been extensively documented in the literature for their applications as antiviral tools in fighting virus infection, including the recent COVID-19 (Xue et al., 2022). Primarily, the small size of carbon-based materials enables them to effectively interact with viruses at the nano-scale level through a biochemical mechanism. This property makes carbon-based materials a promising antiviral agent due to their unique physiochemical characteristics and virustatic/virucidal properties (Sengupta and Hussain, 2021).

Due to their fascinating properties, CQDs and GQDs (**Figure 1**) have recently gained widespread attention in the biomedical field (Liu et al., 2020). As a result, they have shown great potential and prospects to be used in the prevention, detection, and antiviral therapy of various virus strains, specifically SARS-CoV-2 (Xue et al., 2022). Furthermore, their sensing capability and antiviral properties can be tuned by the preparation method, as well as post-synthetic functionalization (Belza et al., 2021). Carbon dots have also been reported to have virucidal properties as they can directly attack the virus (Innocenzi and Stagi, 2020). These findings show the high potential of CQDs and GQDs as antiviral substances, particularly in combating deadly viruses like SARS-CoV-2. CQDs were first discovered in 2004 by Xu et al. (2004), and since then, research and development on CQDs and GQDs have expanded to various fields such as biology, sensors, nanomaterials, energy, and catalysis (Zhou et al., 2011). Previously, CQDs and/or CDs were classified as quantum dots, and the term CQDs started to be widely applied in the 2010s, based on a literature search. To date, many significant advances in the applications of CQDs/GQDs in antiviral aspects have been achieved. In this mini-review or perspective, we present a recent overview and update on the applications of CQDs/GQDs as antivirals, directly and indirectly, to work on the SARS-CoV-2 virus. Both CQDs and GQDs have been successfully applied as biosensors and antiviral substances in the treatment of COVID-19.

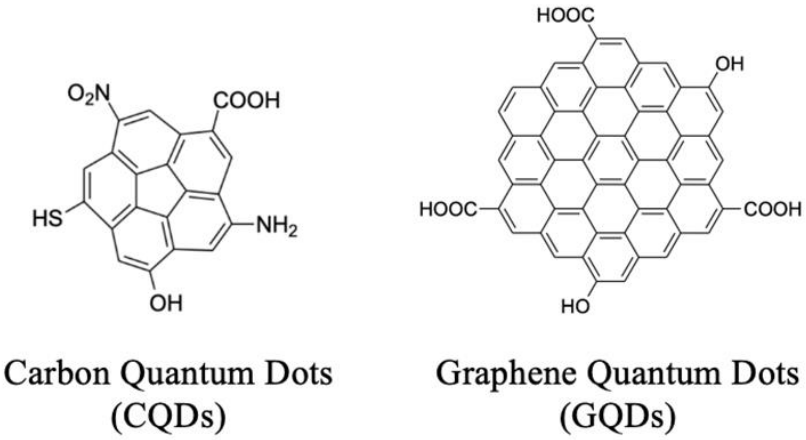

Figure 1 Basic structures of CQDs (Left) and GQDs (Right)

2.0 APPLICATION OF CQD AND GQD AS BIOSENSORS

As commercially available antiviral drugs to treat the COVID-19 disease are limited and most of the drug's approval was based on emergency used authorization (EUA), it is essential to have a rapid and highly sensitive detection of the virus to control the pandemic (Waller et al., 2022). For the transmission of the virus, the spike (S) protein (**Figure 2**: Left) of the respective virus is the key glycoprotein for the entry of the virus into the host cells (Wang and Xiang, 2020). The virus will be bound to the human ACE2 receptor via the receptor binding domain (RBD) (**Figure 2**: Right). Hence, it can be the prominent biomarker for the detection of the virus.

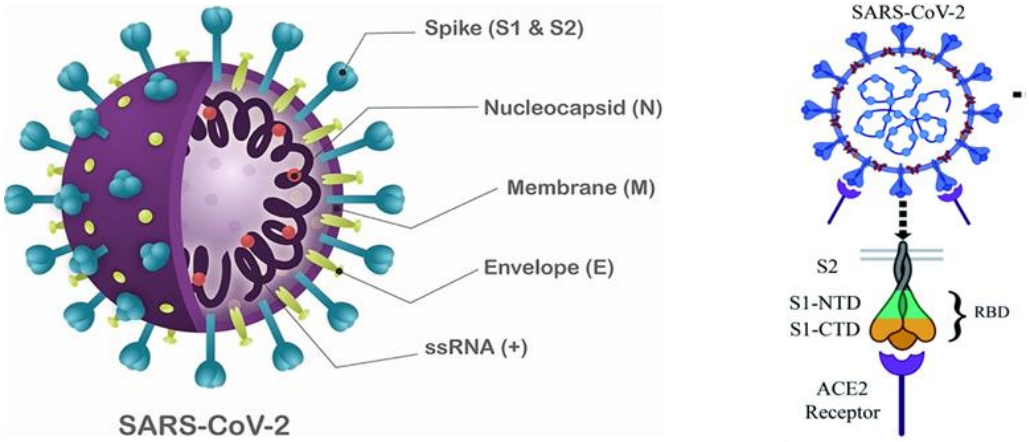

Figure 2 (Left) Illustration of SARS-CoV-2, with its structure consisting of proteins named spike (S), membrane (M), envelope (E), and nucleocapsid (N). This figure (Santos et al., 2020) was reproduced from an open-access article published by Frontier Media S.A. under a Creative Commons Attribution license (CC BY). (Right) The binding of SARS-CoV-2's Spike protein to the ACE2 receptor in human host cells. This figure (Patel et al., 2021) was reproduced from an open-access article published by the Royal Society of Chemistry under a Creative Commons Attribution license (CC BY).

Several sensing techniques such as optical and electrochemical have been reported. For example, CQDs have been reported to be modified with cadmium telluride in the detection of human immunodeficiency virus (HIV) (Liang et al., 2017). Moreover, the fluorescence properties of CQDs can be significantly improved by using the surface plasmon resonance technique (SPR). By adopting this strategy, CQDs would be required to be modified with materials with tunable localized SPR effect. For instance, Achadu et al. (2020) modified CQDs with molybdenum trioxide quantum dots (MP-MoO_3 QDs). Principally, the absorption spectra of MP-MoO_3 QDs would overlap with the fluorescence spectra of CQDs. The overlapping of the two QDs would result in the SPR effect and energy transfer process and thus, enhancing the fluorescence of CQDs. In the detection of the virus, the CQDs-based sensor was able to provide a wide detection of up to 25,000 PFU mL^{-1} of the Influenza A virus, with an LOD of 45 PFU mL^{-1} (Achadu et al., 2020).

The electrochemical method for the detection of the virus is also among the widely applied method when involving nanomaterials as sensors. The large surface area possessed by CQDs would enable various detection to occur simultaneously (Xue et al., 2022). On the other hand, for electrochemical sensing, it can be observed that the trends are more focused on using GQDs as sensors. The surface of GQDs can be modified with an abundant amount of carboxylic groups to provide a large number of binding sites to capture antibodies. For example, Wang et al. (2013) successfully functionalized GQDs with amino-modified iron oxide for sensing avian leukosis virus subgroup J. In another report, the doping of GQDs with N atoms could offer an enhanced electrochemical property. Moreover, the co-doping with sulphur will result in an effective binding site with gold (Au) nanoparticles. The use of Au nanoparticles (NPs) has an advantage in terms of their properties in providing an ultrasensitive detection of biological compounds (Xu et al., 2014). The addition of polymer matrix such as polyaniline (PANI) to the S, N-GQDs could offer long-term stability and contribute to the interaction between NPs and the matrix. These prepared nanocomposites (Figure 3) for the detection of hepatitis A virus (HEV) demonstrated a sensitivity that is equal to the real-time quantitative reverse transcription-polymerase chain (RT-qPCR) method.

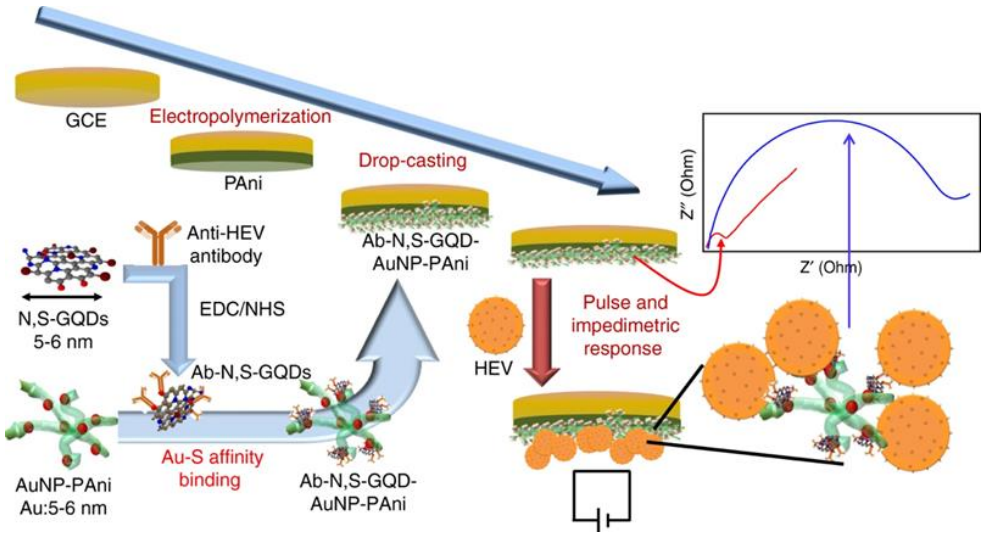

Figure 3 An illustrated representation of the sensor electrode loaded with Ab-N, S-GQDs, AuNP-PANI nanocomposite, and its ability to detect HEV through pulse-induced impedimetry. This figure (Chowdhury et al., 2019) was reproduced from an open-access article published by Springer Nature under Creative Commons Attribution license 4.0 (CC BY 4.0).

In the study conducted by Li et al. (2021), they developed a sensor based on GQDs using the magnetic relaxation switch technique for detecting SARS-CoV-2 directly. To prepare the sensor, they linked the SARS-CoV-2 antibody with magnetic GQDs. The detection process used a closed-tube one-step strategy and homemade ultra-low field nuclear magnetic resonance (ULF NMR) relaxometry operating at 118 μT. The magnetic GQDs-based probe showed exceptional sensitivity owing to its high magnetic relaxivity, with an optimized limit of detection (LOD) of 248 particles/mL. By utilizing this magnetic GQDs-based MRSw with ULF NMR, a secure and highly sensitive detection method for the SARS-CoV-2 virus can be achieved.

Based on the review, it is hypothesized that both CQDs and GQDs have the potential to be functionalized and modified to produce an ultra-sensitive biosensor capable of detecting SARS-CoV-2. Currently, there is limited evidence on the successful development of CQDs and GQDs-based biosensors that can directly detect SARS-CoV-2. Nonetheless, numerous studies have been conducted on biosensor development that is relevant to COVID-19 applications. For instance, there have been reports on the development of CQDs and GQDs-based sensors for measuring the level of interleukin-6 (IL-6) in humans.

Several studies indicate that individuals infected with COVID-19 experience an increase in their interleukin 6 (IL-6) level, and this level is linked to the severity of the disease and mortality (Yonas et al., 2020). An anomalous level of IL-6 (e.g., 1000 pg/mL) can be a warning sign of serious health problems, such as chronic infections or various cancers (Xu et al., 2012). Consequently, precise detection of molecular biomarkers at trace levels is crucial for detecting cancer and treating patients. Mahani et al. (2022) developed an IL-6 aptasensor based on fluorescence resonance energy transfer (FRET), utilizing a DNA aptamer modified with nitrogen-doped CQDs and gold nanoparticles (Au NPs) as a donor-quencher pair. As illustrated in Figure 4, the modified aptamers capable of target recognition were attached to the surface of Au NPs based on Au–S chemistry. The assayed target could disrupt the donor–acceptor assemblies to produce a concentration-related fluorescence recovery of NCDs

with an emission wavelength at 445 nm by using an excitation wavelength of 350 nm. When two different probes were utilized, the interaction between DNA aptamers and IL-6 protein could be studied by adopting FRET efficiency. One of the aptasensors was able to calculate a limit of detection of 0.82 pg/mL and a linear response range of 1.5 - 5.9 pg/mL for IL-6. These studies suggest that the developed biosensor can be further used in determining the level of IL-6 in human serum. Furthermore, the high sensitivity and selectivity as well as the non-complex procedure that could be developed from this experiment is a promising strategy for alternative sensing of IL-6 level in clinical applications.

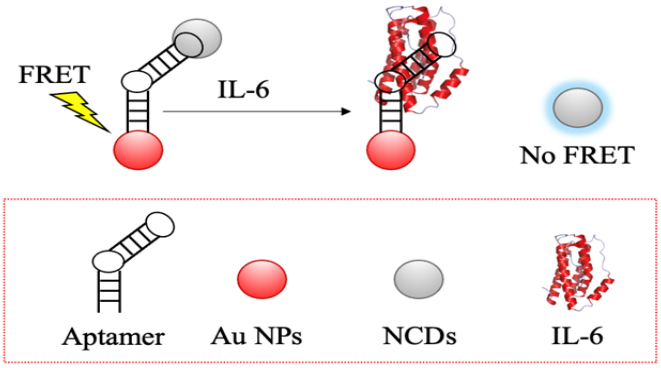

Figure 4 A schematic illustration of FRET-based biosensor for IL-6 detection.

Moreover, the presence and excess drugs for the treatment of COVID-19 in humans have also been successfully detected by both CQDs and GQDs. In another sensor developed by Salman et al. (2022), the CQDs were modified with a polyamine to analyse the presence of molnupiravir (MOL) in real plasma samples (pharmacokinetic) and pharmaceutical tablets. MOL is a drug that currently is used for the treatment of COVID-19. The modified polyamine CQDs were prepared by using apricots as precursors via a one-step synthesis. When the MOL was added, the relative fluorescence intensity (RFI) was successfully quenched by the respective MOL. The limit of detection (LOD) was found to be 1.61 ng mL^{-1} while the linear range was calculated to be in the range of 2 – 70 ng mL^{-1}. The high sensitivity and selectivity demonstrated by the modified CQDs showed that they have a high potential to be applied as sensors in clinical laboratories.

In addition to MOL, doxycycline has also been utilized as a treatment for COVID-19. Nevertheless, the uncontrolled use of doxycycline can cause bacteria and gene resistance, which can negatively impact the treatment of different infectious diseases (Seifert, 2022). To address this concern, Raut et al. (2022) developed a sensor that employs CQDs to detect doxycycline, with ascorbic acid and diethylenetriamine as precursors. The doxycycline was detected based on the fluorescence quenching technique and the quenching mechanism of doxycycline was attributed to what the author described as static quenching and inner filter effect (IFE). The developed CQDs-based sensor was highly sensitive as the LOD was calculated to be 0.25 mM. Hence, the high potential of this sensor extends beyond COVID-19 treatment, as it can also be employed in various biomedical applications, including the identification of doxycycline in pharmaceutical waste and bacterial cells. Additionally, due to its high sensitivity, the sensor could be used in environmental monitoring. Another repurposed drug for COVID-19, nitazoxanide (NTX) is also widely used in the treatment of COVID-19. Qandeel et al. (2023) developed a CQD that was modified with sulphur and nitrogen to detect the drug. As a result, the developed modified CQDs were capable to detect the presence of NTX with an LOD of 0.07 mM and in a concentration between 0.25 and 50.0 mM.

3.0 APPLICATION OF CQDs AND GQDs IN COVID-19 TREATMENT

In the prevention and treatment of COVID-19, one common approach used is to either inhibit the angiotensin-converting enzyme 2 (ACE2) receptors or protect the receptor-binding domains (RBD) present in the S1 protein of COVID-19. Another strategy involves the cleavage of the S2 protein site, which is used by the host cell's furin enzyme to activate the virus (Ramezani et al., 2021). The high surface-to-volume ratio possessed by CQDs can provide a space for the attachment of ligands, thus, blocking viral entry into the cell (Kim et al., 2021). For example, Łoczechin et al. (2019) studied the antiviral activity of functional CQDs prepared from ethylenediamine/citric acid towards human coronavirus HCoV-229E. The prepared CQDs demonstrated a concentration-dependent virus inactivation with an estimated EC_{50} of 5.2 ± 0.7 mg mL^{-1}. However, when postmodified with boronic acid ligands, the concentration-dependent virus inactivation (EC_{50}) was found to be 52 ± 8 mg mL^{-1}. This shows that the CQDs could inhibit the entry of HCoV-229 via the interaction of the functional groups present on CQDs with the virus entry receptors. Moreover, large inhibition activity was observed at the viral replication step. The binding of the HCoV-229E virus to the host cell is shown in Figure 5 while inhibition of interaction and viral replication by functional CQDs are illustrated in Figures 5(a) and (b). These results demonstrated that functionalized CQDs with a modification of the ligand are capable of interfering with viral attachment to cells and reducing viral replication. As such, this approach can reduce viral infection and viral spreading. Hence, this approach can be used to target SARS-CoV-2 as the respective virus of HCoV-229 has high similarities with the SARS-CoV-2 virus.

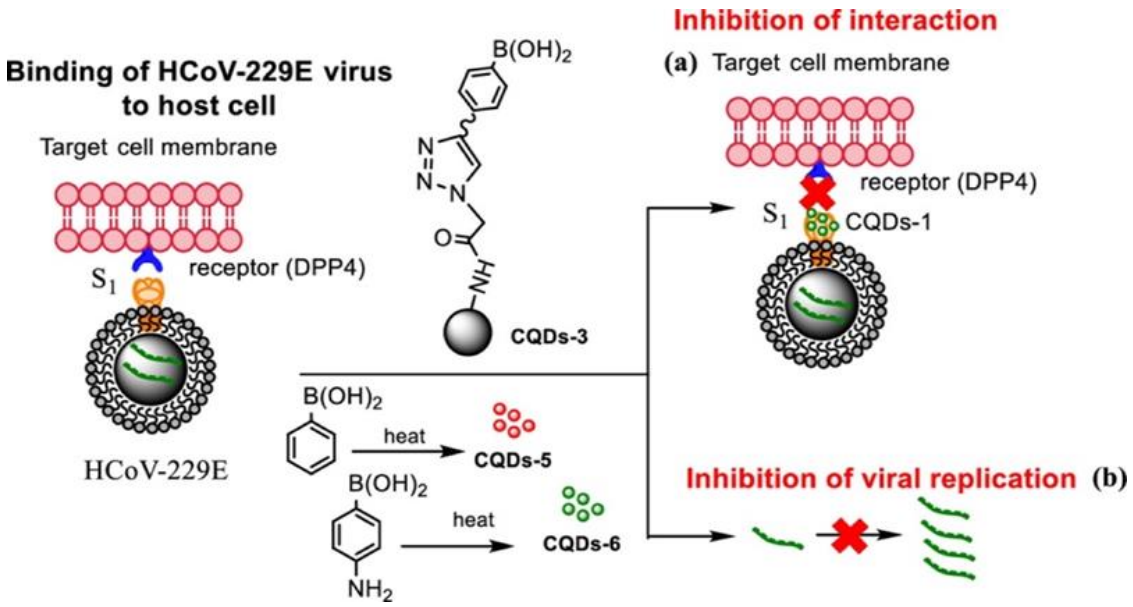

Figure 5 Illustration of the binding between HCoV-229E virus and host cells. (a) Schematic illustration in which the CQDs inhibit the interaction between HCoV-229E virus and host cells and (b) inhibition of viral replication (Łoczechin et al., 2019). This figure was reproduced (adapted) from the American Chemical Society under the ACS COVID-19 subset for unrestricted research re-use and analyses.

According to Ramezani et al. (2021), in silico study indicate that CQDs functionalized with OH and amine groups exhibit a high affinity for binding to the RBD of the S protein of COVID-19, as well as the ability to block the S2 cleavage site. These findings suggest that these functionalized CQDs have the potential as therapeutic agents. They found out that the presence of functional groups on the CQDs can affect the interaction between CQDs and the virus, thus, influencing its effectiveness. Figure 6 shows the molecular docking between functionalized CQDs and RBD. For example, OH-CQDs have the highest binding energy (-699.3 kJ.mole^{-1}) towards the virus compared to others such as NH_2-OH-CQDs (-592.2 kJ.mole^{-1}) and EtOH (-148.5 kJ.mole^{-1}). However, NH_2-OH-CQDs have the highest binding percentage (85%) with RBD and EtOH has up to 84% binding percentage with the RBD. Meanwhile, OH-CQDs have up to 80% of binding percentage with RBD. The results indicate that the size and molecular weight of functional groups/ligands can affect the interaction between CQDs and the SARS-CoV-2 virus. Specifically, larger sizes or molecular weights are associated with higher binding energies.

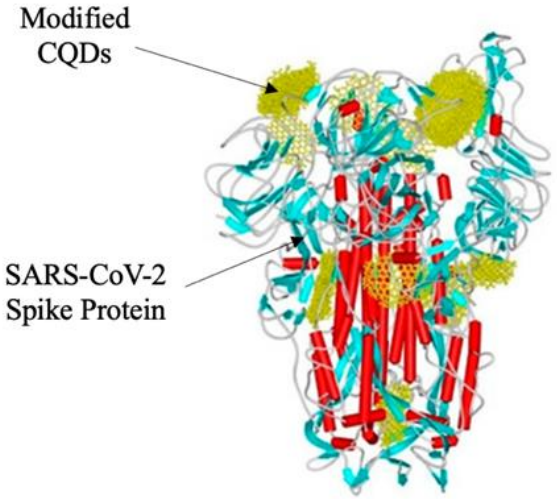

Figure 6 Interaction of modified CQDs with SARS-CoV-2 S protein using MD simulation (Ramezani et al., 2021). This figure was reproduced from an open-access article published by MDPI under a Creative Commons Attribution licence 4.0 (CC BY 4.0).

Kalkal et al. (2021) proposed the modification of CQDs and Allium Sativum (AS) as a potential theranostic agent to fight against SARS-CoV-2. AS is selected owing to its effective dietary supplement and demonstrated antibacterial, anti-inflammatory, and immune-modulatory properties (Suleria et al., 2015). For that reason, AS extracted compounds may play a

role in modulating the secretion of cytokines, which is the primary mechanism underlying the therapeutic modulatory effects. For CQDs, modification of CQDs using the heteroatom doping technique can have a significant effect in reinforcing their antiviral properties (Xue et al., 2022). In addition to doping, functionalizing CQDs can provide numerous benefits, allowing them to disrupt the interaction between viruses and host cells (Garg et al., 2020). For instance, Ting et al. (2018) developed cationic CQDs that were shown to prevent viruses from entering cells by modifying the structure of surface proteins on the viruses. The anti-viral effect of the porcine epidemic diarrhoea virus, which mimics the SARS-CoV-2 model, was evaluated using the prepared CQDs. As a result, the viruses were agglomerated, leading to the inhibition of negative-strand RNA synthesis and the accumulation of reactive oxygen species. Furthermore, the modified CQDs induced the production of pro-inflammatory cytokines and interferon-stimulating genes (ISGs), thereby impeding viral replication (**Figure 7**). Hence, it is envisioned that CQDs could be a highly effective antiviral agent. Functionalizing AS with CQDs can also be further developed as a therapeutic agent with dual purposes. The AS is effective against viral fevers, colds, and influenza in both pre-clinical and clinical trials, providing strong evidence for its use in clinical settings.

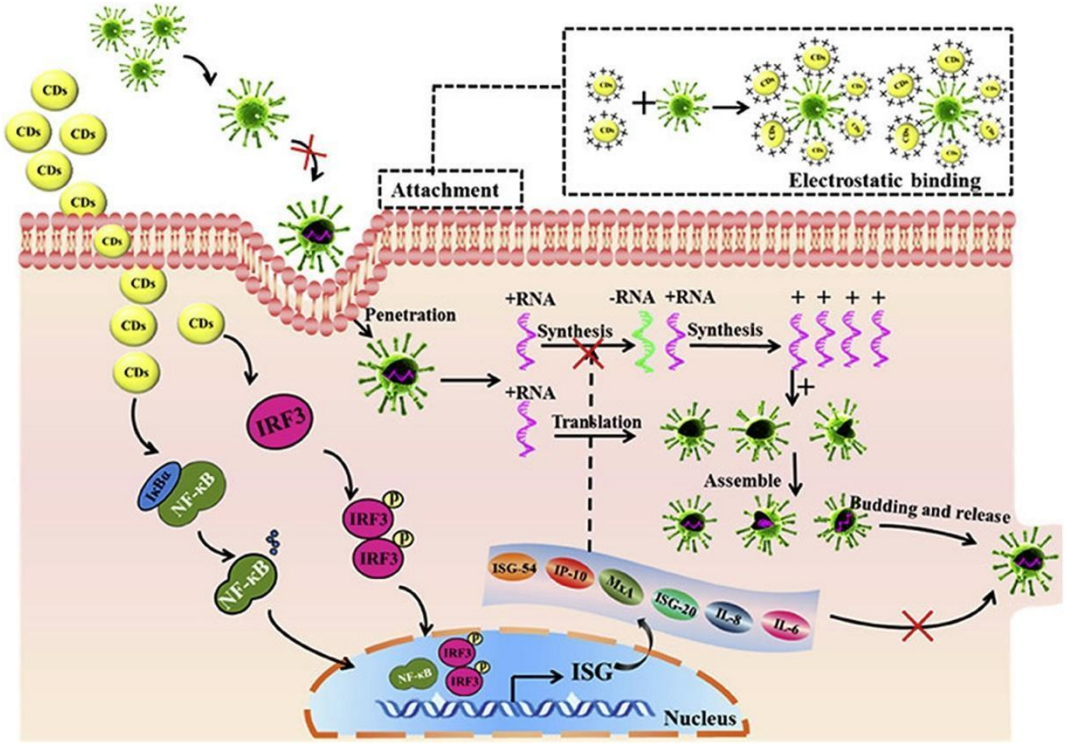

Figure 7 Viral infection mechanism using CQDs/CDs. Reprinted with permission (Ting et al., 2018). Copyright (2018) American Chemical Society.

In terms of GQDs, they are composed of a graphene lattice and consist of single fragments of graphene that display luminescence properties that are dependent on their size. These properties arise from the quantum confinement effects and edge effects of the GQDs. (Li et al., 2013). As a result of their unique optical properties, they have become a prospect in the application of nanosensors, biosensing and other related biomedical applications, specifically in combatting COVID-19 disease (Xue et al., 2022). In a work by Pramanik et al. (2022), a modified form of GQDs was developed by conjugating them with human host defence peptides, including neutrophil a-defensin HNP1 and human cathelicidin LL-37. This modification was aimed at inhibiting the entry of the delta variant (B.1.617.2) of SARS-CoV-2. The modified GQDs have been demonstrated to prevent the binding of virus spike protein RBD with the host cell' ACE2. Quenching mechanisms showed a non-linear Stern-Volner quenching profile, suggesting the presence of a multibed binding site with GQDs. According to experimental data, the fluorescence signal from GQDs was observed to immediately quench due to the binding between the bioconjugate GQDs and the RBD spike protein of the delta variant in its presence.

Recently, Hsieh et al. (2023) developed nitrogen-functionalized GQDs as an antiviral nanomaterial for the treatment of Feline coronavirus NTU156 (FCoV NTU156) and Enterovirus 71 (EV71). They showed that the surface functionality of GQDs significantly contributed to the interaction of GQDs and RBD of the spike protein. Moreover, the addition of polyethylene glycol has improved the adsorption of GQDs onto the surface of the virus, resulting in enhanced virus inhibition. This remarkable viral inhibition shown by the prepared functionalized GQDs can be applied in personal protection equipment (PPE) by spraying on different substrates as a disinfectant to protect against viruses such as SARS-CoV-2.

The low toxicity of GQDs and their hydrophilic properties have led to the development of GQDs in drug delivery applications. The modification and functionalization of GQDs with amine and carboxyl groups demonstrated that their toxicity was relatively lower compared to graphene oxide (GO) and reduced graphene oxide (rGO) (Alemi et al., 2020). The prospect of GOQDs as drug delivery to treat COVID-19 disease was investigated by Shahabi et al. (2020). The potential of GOQDs to deliver the drug for COVID-19 treatment was evaluated *in silico* by using molecular dynamics (MD). In the study, carmofur was

used as a potential drug since it has been reported to be a promising treatment for SARS-CoV-2 due to its half-maximal effective concentration (EC_{50}) value of 24.30 mM. MD simulation demonstrated that the presence of p-p stacking and hydrogen bonding have significantly stabilised the GOQDs-Carmofur complex. The spontaneous attraction of GOQDs-Carmofur complex with the main protease (M_{pro}) has led to the penetration of Carmofur into the active catalytic site. The results demonstrate that GOQDs could be an effective carrier for loading and delivering Carmofur. These findings suggest that GOQDs have potential applications as drug delivery systems for treating diseases caused by viral infections.

Gene therapy that uses mRNA or plasmid DNA (pDNA) has gained attention due to its ability to express desired proteins in the body by transcribing and translating their corresponding sequence information into therapeutic proteins that can help fight various diseases (Franck et al., 2021). As functionalized GQDs exhibit low toxicity that enables them to the application biomedical, various researchers have attempted to improve their biocompatibility and reduce toxicity for in vivo applications (Karki et al., 2020). For example, Ahn et al. (2021) developed N-GQDs for a novel application as transfection agents for mRNA and pDNA. To achieve that, the GQDs must be functionalized to enable the electrostatic interaction with the genes or therapeutic molecules. The positively charged NGQDs were prepared by using the microwave-assisted hydrothermal method and would electrostatically interact with the negative charge of mRNA and pDNA. Based on the flow cytometry analysis and fluorescence micrograph of HeLa cells (**Figure 8**), the positively charged NGQDs were confirmed to have electrostatically interacted with the model mRNA and pDNA. This suggests that the NGQDs have successfully transfected the cells and based on their comparable performance to Lipofectamine, it is expected that the NGQDs can be soon applied in the clinical field as transfection agents after consideration of their toxicity and metabolism.

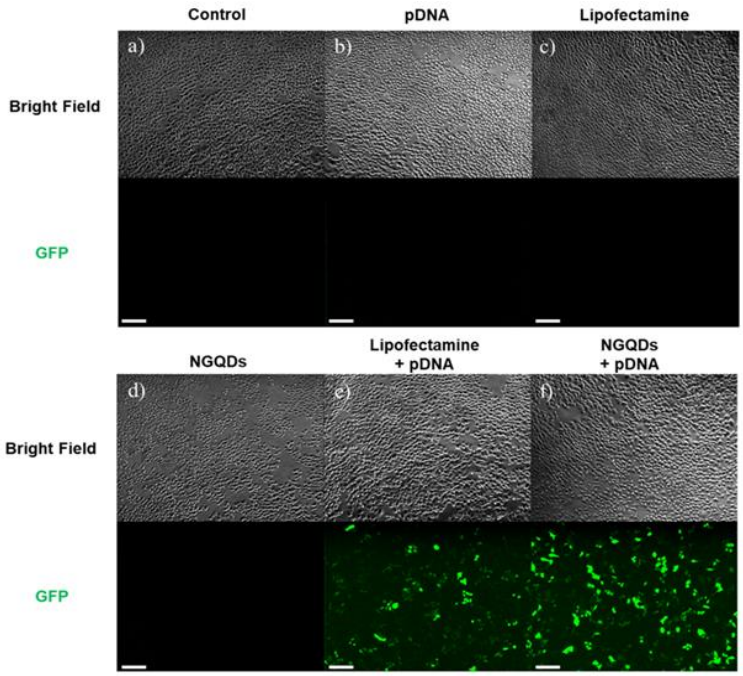

Figure 8 The micrograph of HeLa cells after 24 h transfection with (a) control, (b) pDNA only, (c) Lipofectamine only, (d) NGQDs only, (e) Lipofectamine + pDNA complex, and (f) NGQDs + pDNA complex, under a fluorescence microscope. This figure was reproduced from an open-access article (Ahn et al., 2021) published by MDPI under a Creative Commons Attribution licence 4.0 (CC BY 4.0).

4.0 CONCLUSION

In summary, SARS-CoV-2 has created a medical emergency due to its deadly and highly contagious nature. Although the world at the moment has progressively shifted from the pandemic to the endemic phase, we must prepare for the deadly virus that might cause an outbreak in the future. Therefore, nanomaterials like CQDs and GQDs can be further explored and developed to fight against deadly viruses like SARS-CoV-2. In this mini-review, both CQDs and GQDs have shown promising results against SARS-CoV-2, particularly in sensing and medical treatment. Based on the recently published reports, functionalization of CQDs and GQDs is required to improve biocompatibility and reduce toxicity. Both CQDs and GQDs work well as antiviral substances, particularly in inhibition of the virus entry by blocking the spike protein from binding and interacting with ACE2. Moreover, modification with herbal sources like AS can be promising because of their biocompatibility and strong antiviral properties. Other than direct application to COVID-19, both materials can be used as a sensor to detect the excessive presence of antiviral drugs such as MOL and doxycycline. Although the results were promising, further research is required to address some issues. For example, the mechanism of how the antiviral activity takes place must be elucidated and explored. Moreover, the toxicity or cytotoxicity properties of CQDs and GQDs must first be made known to ensure it would be less harmful to humans.

Nevertheless, both CQDs and GQDs hold a bright prospect as bionanomterials to fight against COVID-19 and other potential deadly virus in the future.

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