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Carbon-based nanomaterials against SARS-CoV-2: Therapeutic and diagnostic applications

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ABSTRACT

COVID-19, which was first spread in China in 2019 and consequently spread worldwide, is caused by the SARS-CoV-2. Today, various carbon-based nanomaterials such as graphene, graphene oxide, carbon dots, and carbon nanotubes have been explored for the specific detection and targeted inhibition/inactivation of SARS-CoV-2 due to their great surface chemical structures, easy to-functionalization, biocompatibility, and low toxicity. According to exclusive inherent properties, carbon-based nanomaterials are promising candidates for targeted antiviral drug delivery and the inhibitory effects against pathogenic viruses based on photothermal effects or reactive oxygen species (ROS) formation. These high-stability nanomaterials exhibited unique physicochemical properties, providing efficient nanoplatforms for optical and electrochemical sensing and diagnostic applications with high sensitivity and selectivity. Up to now, these materials have been used for the fabrication of diagnostic kits, different types of personal protective equipment (PPE) such as anti-viral masks, vaccines, self-cleaning surfaces, and other subjects. This review article explores the most recent developments in carbon-based nanomaterials' diagnostic and therapeutic potential towards SARS-CoV-2 detection and inhibition, different mechanisms, challenges and benefits of the carbon-based nanomaterials.

1. Introduction

Given that SARS-CoV-2 has become worldwide since the end of 2019, there is a need for research and production of novel materials, vaccines, and drugs that are effective in identifying, preventing, and treating this pathogenic virus. Although advances have been made in this area, whether in the development of diagnostic methods, vaccine and drug production and to some extent, the immunity to the virus has been achieved so far, but the virus still plagues the world. There is a major concern about the quick spread of SARS-CoV-2, which can be with a range of other pathogenic microorganisms, such as those which are multidrug-resistant. Thus, the coincidence of

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COVID-19 with other infectious diseases (especially COVID-19, drug-resistant microbial infections) establishes a life-threatening condition for humans. Several medications such as favipiravir, interferon β−1a, and elisidepsin have been suggested [1,2]. It requires developing more up-to-date techniques to fight coronaviruses and the spread of similar viruses such as monkeypox. Different therapeutic techniques are progressive to recognize effective drugs and vaccines to treat COVID-19 [3,4]. Techniques based on nanotechnology can be arranged to manipulate and evolve advanced antiviral delivery systems, nano-based drugs, and nanosensors [5,6]. Carbon-based nanomaterials with exclusive properties can contribute to the progress of diagnostic sensors with great sensitivity/selectivity and simplicity to the economic diagnosis of COVID-19 with a small size (20–400 nm). Due to the nano-sized structure of carbon-based nanomaterials (zero, one, and two-dimensional) and their optical/electrical properties, they are promising nanomaterials to combat COVID-19.

Carbon-based nanomaterials exhibited potential antiviral activity against SARS-CoV-2, with low toxicity and multifunctionality properties [7,8]. The development of these nanomaterials as antiviral agents after suitable modification or interaction with compatible polymers can provide advanced systems with improved compatibility and therapeutic efficacy [9]. Besides, carbon-based nanomaterials have a great surface area permitting their functionalization or interaction with suitable biocompatible or bioactive agents (such as chitosan, cellulose, alginate, etc.), which can improve their targeting properties and biosafety [9]. On the other hand, these nanomaterials can aid in the development of targeted drug delivery systems against COVID-19 due to their unique chemical structures without prompting reticular endothelial cells' immune response; their large surface area can help to increase the drug loading capacity. Besides, they are able to pass through membranes with negative charges due to the change of their own surface charge [10].

One of the most explored carbon-based nanomaterials is graphene and its derivative. Graphene is a single-atom-thick carbon layer with good electrical conductivity and is arranged in an sp^2 carbon construction. Graphene exhibited a high surface area according to a single layer of carbon atoms, leading to single-molecule detection. The formation of a sensor occurred with the binding of a biomolecule with the surface of graphene. They can interact with light and are capable of absorbing visible light. This activity has a significant role in the generation of heat. Besides, the application of reduced graphene oxide (rGO) can provide a high hydrophilic surface for the adsorption of nucleic acids and proteins, showing more antimicrobial and anti-viral activities.

The properties of CNTs, such as low density, flexibility, and excellent mechanical strength, make them suitable for the detection and inhibition of SARS-CoV-2. These nanomaterials are resistant to most acids and bases and have high photothermal conversion efficiency and capacity to form reactive oxygen species (ROS). They have been applied in diagnosis and drug/gene delivery modalities to combat various viruses, such as SARS-CoV-1 [11,12]. On the other hand, quantum dots (QDs) have exclusive properties permitting their applications for the greater sensitive diagnosis and inhibition of SARS-CoV-2. Through the conjugation of QDs with the size of 1–10 nm with fluorescent probes, they were developed for fluorescence imaging of different cellular procedures. Besides, carbon QDs (CQDs) have shown different benefits of cost-effective synthesis methods, low toxicity, and photoluminescence properties, which can be applied as attractive alternatives against viruses [13–15]. The combination of carbon-based nanomaterials (especially QDs) with different metallic nanoparticles (NPs) has also been employed for the development of point-of-care testing (POCT) to a quick diagnosis of SARS-CoV-2, showing great potentials in commercial scale production, By applying QDs, several successful results were obtained regarding the single molecular tracking using their extended fluorescence lifetime [16]. In addition, fullerene and its derivatives were deployed with suitable antiviral activities against HIV [17]. Fullerene, such as C_{60} fullerene, acts as an enzyme inhibitor, and also can be employed as drug delivery carrier. According to the existence of electron-deficient chemical bonds in the structure, C_{60} fullerene simply ascribes free radicals, capable of effectively showing the anti-inflammatory and antiviral activities [18].

Numerous articles have been published pertaining to the detection and treatment of COVID-19 using nanomaterials [19–22]; Herein, most recent advancements pertaining to the applications of carbon-based nanomaterials for specific diagnosis, inhibition, and treatment of COVID-19 are deliberated with a focus on their significant limitations, challenges, and future perspectives; the significant roles of computational methods in the fight of SARS-CoV-2 using carbon-based nanomaterials are highlighted.

2. Carbon-based nanomaterials against SARS-CoV-2: synthesis, diagnosis and prevention

Recently, carbon nanomaterials can be provided as allotropes such as graphene, diamond, CNTs, and C60, as well as carbon dots (CDs) for several electrochemical, biosensing, energy conversion, and drug delivery applications. These types of nanomaterials can be categorized into zero-dimensional (0D) nanodots, one-dimensional (1D) nanotubes, two-dimensional (2D) and three-dimensional (3D) materials [23]. Since the properties of carbon-based nanomaterials are frequently dependent on their atomic structures and interactions with other materials, significant recent studies and determinations have been made to the bulk synthesis of homogeneous materials and their assembly in bulk-scale [24,25]. These nanomaterials can be synthesized by a variety of top-down and bottom-up approaches [26]. In the top-down method, a precursor material is cut into the nanoscopic size by using different chemical and physical procedures. In the top-down techniques, the breakdown of carbonaceous materials such as CNTs, graphene, GOs, and fullerenes can be performed through different procedures such as electrochemical oxidation, liquid Phase exfoliation, chemical ablation, and laser beam/ion beam treatment [27]. The bottom-up assays use atomic precursors to synthesis nanocarbon materials. Using the bottom-up methods, GQDs are synthesized from pyrolysis or carbonization of precursor molecules [28]. Bottom-up assays comprise pyrolytic procedures, hydrothermal and solvothermal methods, and microwave-assisted method [29]. Chemical vapor deposition (CVD) is recognized as the most efficient bottom-up method to synthesize cost-effective and controllable synthesis of graphene *via* a great surface area. The formation of a single atomic layer graphene film on Ni requires annealing polycrystalline Ni in the atmosphere at 1000 °C to enhance grain size through exposure to the H_2/CH_4 gas mixture [30]. Researchers described a method for the size-controlled production of the GQDs with the use of the self-assembled block copolymers (BCP), which are applied as the etch mask on the graphene films enhanced by the CVD. Although this method attained a lower yield, the condition produced the highly smooth

Table 1
Different types of biosensors based on carbon-based nanomaterials with their advantages and limitations for specific detection of SARS-CoV-2.

Biosensors	Nanomaterials	Targeted area	Functions	Advantages	Limitations	Refs.
SERS Biosensor	GO	Viral oligonucleotides	Detection of COVID-19 by DNA/GO/AuNP	High sensitivity	Low sensitivity	[45]
Fluorescence-based Biosensors	CNTs	Spike protein RBD Nucleic acid sequence	ACE2-SWCNT nanosensor can interact with a protein of the virus, RBD, causes a strong turn-on fluorescence response The destroyed probe by using CRISPR/Cas13a cannot be detected on an immunochromatographic strip using QDs	Fast response Simple instrument, Multiple analysis	Long-time for scalable fluorescence Low sensitivity	[46] [47]
FET Biosensor	Graphene	Virus genome	The ability of graphene to adsorb ssDNA according to π–π bonds	High sensitivity/selectivity	Needs reliable system	[48]
Electrochemical Biosensors	CNTs	Atigen nucleocapsid protein, Specific immunoglobulins , C-reactive protein (CRP)	The use of capture antigens and antibodies immobilized on laser-engraved graphene (LEG)29,30 electrodes	High sensitivity Rapid detection	The need to modify the platform to quickly and specifically diagnose the SARS-COV-2	[49]
Electrochemical Biosensors	Graphene/GO/Rgo/CNTs	S1 and N protein RBD S-RBD protein	The electrochemical assay was developed in order to S or N protein detection using magnetic beads as support of antibody with alkaline phosphatase as immunological label Immobilization of the thiol-terminal aptamer probe on the surface of the CSPE/CNF–AuNP, and measurement of SARS-CoV-2-RBD with the LOD of 7.0 Pm Production of cobalt-modified TiO_2 nanotubes (Co-TNTs)-based electrochemical biosensor in order to highly sensitive detection of virus, based on the production of a complex among the Co and the biomarker at a specific voltage, due to the decreases of Co ions and oxidation of the biomarker	Low power consumption High sensitivity low-cost fabrication	Bulky size Need for external power source	[50] [51] [52]

LOD: Limit of detection, CSPE: Carbon-based screen-printed electrode/CNFs: Carbon nanofibers, RpGO: Porous reduced graphene oxide, TB: Toluidine blue; LSPR: Localized surface plasmon resonance; SERS: Surface-enhanced Raman scattering biosensors; RBD: receptor-binding domain. GO: Graphene oxide; FET: Field-effect transistor

particles [31]. CNTs are exceptional materials with good chemical/physical and electrical properties. CNTs can be synthesized with different methods, such as laser ablation and CVD [32]. In the company of the common chemical methods, green synthesis methods have been widely studied according to their cost-effectiveness, ease of synthesis, and environmentally benign properties. On the other hand, doping carbon nanomaterials with different metal and organic materials provide remarkable optical, electrical, and biological properties. For instance, the techniques for the synthesis of doped GQDs are significant for versatile applications [33].

In general, given the appearance of the greatly transmissible strains of coronavirus, there is a high clinical requirement for cost-effective, large-scale, and point-of-care testing and sensing devices and techniques for the SARS-CoV-2 [34]. Various detection methods have been established to diagnose SARS-CoV-2, including nucleic acid amplification methods with several rat-based polymerase chain reaction (PCR) tests and CRISPR/Cas9 techniques [4,35,36]. Current COVID-19 testing approaches can be categorized into serological and molecular tests. Molecular tests persist in diagnosing coronavirus by detecting CoV-2 RNA. Besides, reverse transcription (RT)-PCR acts as a common detection test based on viral genes and is presently the greatest extensive assay in the COVID-19 detection [4]. This technique is expensive ($10 per test) and takes a long time, between 1 and 3 h. Until now, RT-PCR tests can be employed with sensitivity in recognizing viral particles, with the limit of detection (LOD) of 1 and 10 viral RNA copies [37]. Serological tests identify the presence of antibodies in blood serum [38]. The distinctive requirements for devices and their high cost have made the commercialization of RT-PCR difficult in underdeveloped zones such as Africa. Similar challenges happen to droplet digital (dd) PCR and next generation sequencing (NGS) tests. Thus, we need novel and more accessible nanoplatforms with low cost and simplicity to overcome these challenges regarding the specific detection of SARS-CoV-2 or other pandemic infections [39,40].

Nano-based biosensors, which are applied to detect the presence of different biomolecules or microorganisms, work by amplifying small amounts of the signal based on the transduction. Various types of biosensors have been developed based on the detection assay, including optical sensors, and electrochemical, thermal biosensors, and mechanical biosensors (Table 1). Carbon-based nanomaterials

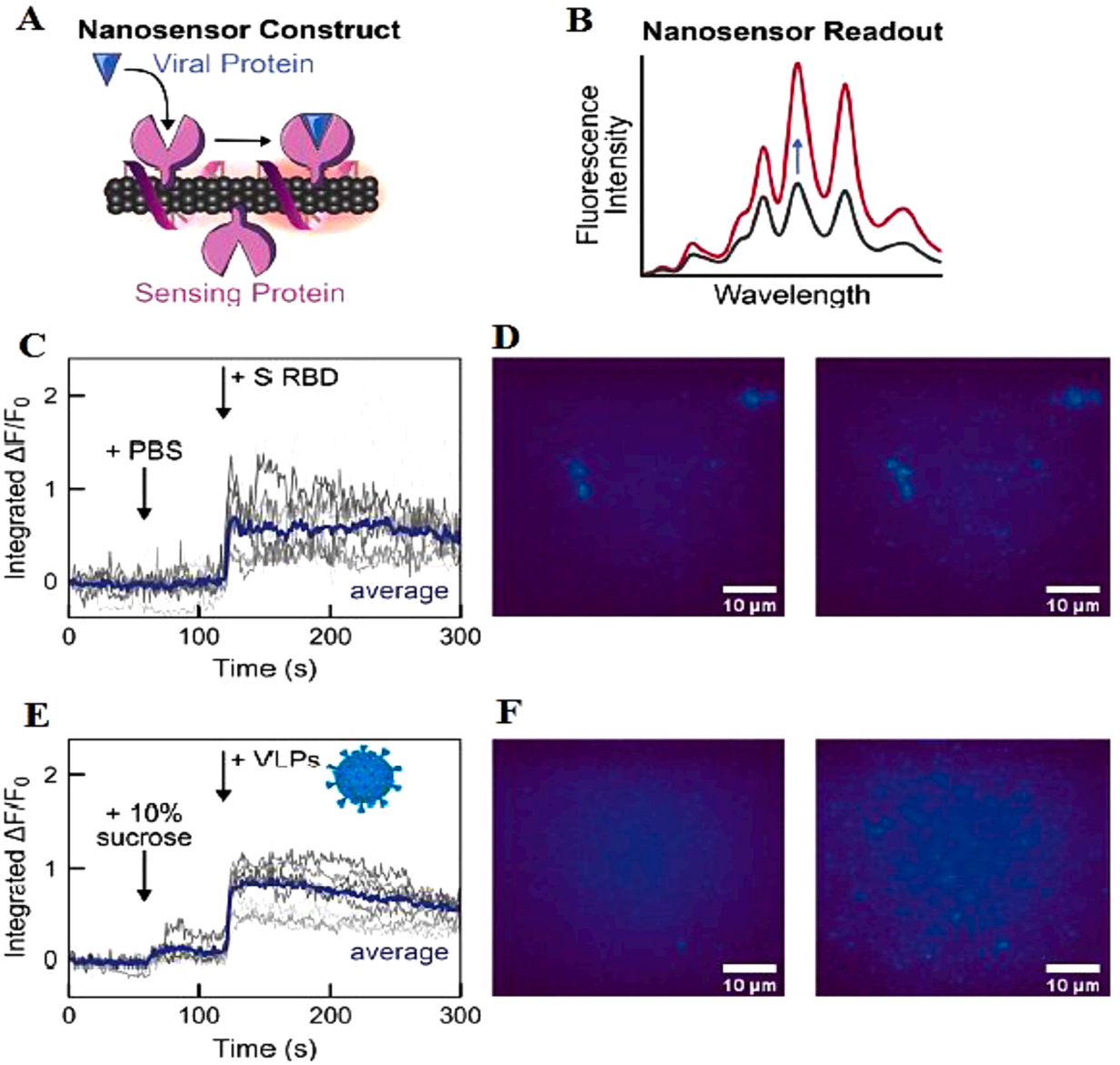


Fig. 1. (A, B) The quick virus spike protein detection through CNTs -based Near-Infrared Nanosensors. Surface-immobilized ACE2-SWCNT nanosensor (A-D) Addition of PBS at 1 min triggered no alteration in fluorescence. The addition of S RBD at a short time produced a turn-on fluorescence response. (D-F) The addition of sucrose buffer at 1 min produced a small increase in fluorescence. Reproduced with permission from Ref. [46].

can be applied in designing highly sensitive nanosensors, smart nanocarriers, and "next-generation" vaccines [41]. These types of nanomaterials mostly contain carbon and are biodegradable and biocompatible, showing promising tissue regeneration/engineering potentials [42]. Carbon-based nanomaterials exhibited fascinating benefits and unique properties for biosensing applications, such as large surface area, great electrical conductivity, high biocompatibility, and mechanical strength [43]. On the other hand, the great electronic conductivity resulting from the exclusive structures of carbon nanomaterials, such as CNTs, makes them suitable for their use in transducers of sensors, which convert the identification of a target into an electrical signal. Although, a great specific area is promising for immobilizing a high amount concentration of functional units on the surface of the nanomaterial, which identifies the target analytes in the biosensors [44]. In addition, with the recent advances in synthesis assay, characterization/modification techniques, carbon-based nanomaterials can be applied as attractive candidates for different types of scalable technologies, particularly in the inactivation of coronavirus and the development of point-of-care systems [9].

2.1. Optical biosensors

Optical nanosensors are one of the significant classes of biosensors being established for rapid and specific detection of pathogenic

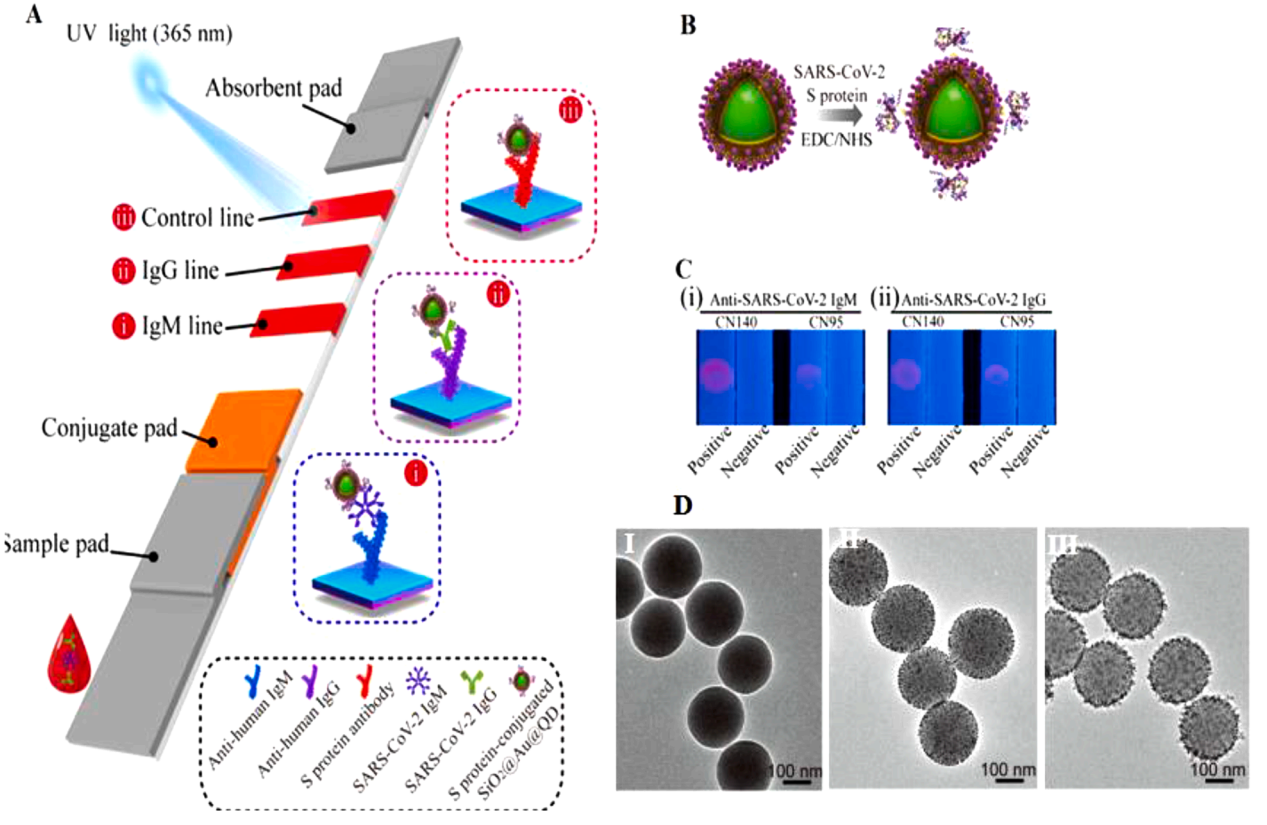


Fig. 2. (A) The LFIA sensor or diagnosis of COVID-19. (B) The S protein-conjugated SiO_2@Au@QD. (C) Optimization of NC membrane of LFIA. (D) TEM images of (I) SiO_2 (~200 nm), (II) SiO_2@Au, and (III) SiO_2@Au@QD. Reproduced with permission from Ref. [60].

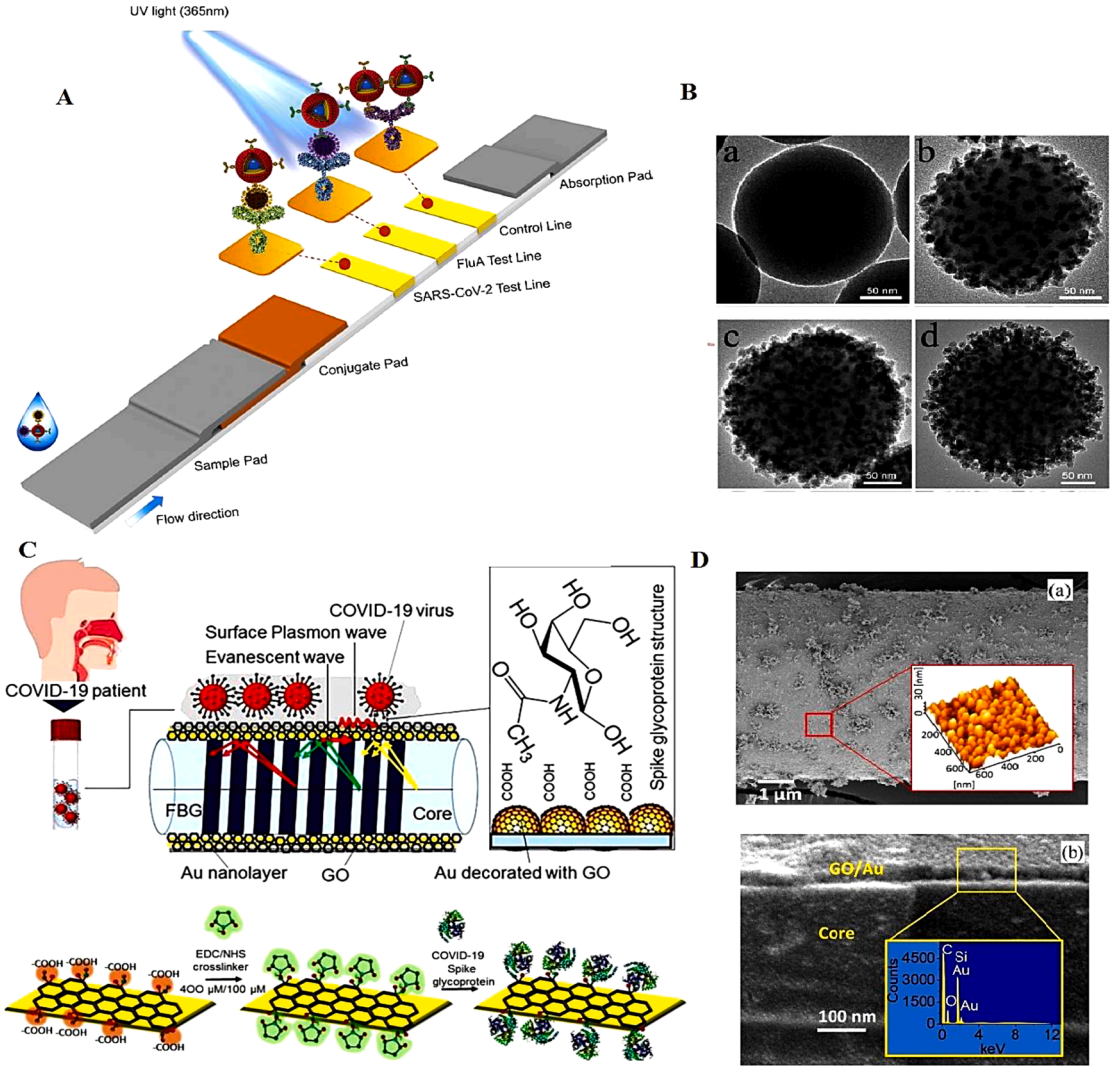


Fig. 3. (A) Production of SiTQD probes and their use in order to detection of the virus. (B) TEM images of (a) SiO_2 core (~180 nm), (b) SiQD, (c) SiDQD, (d) SiTQD nanomaterials (240 nm) Reproduced with permission from Ref [61]. (C) Connecting of the spike glycoprotein of virus with GO (D) FESEM image of the GO-decorated Au/FBG probe (a) and synthesis of GO-decorated Au film on the FBG fiber (b). Reproduced with permission from Ref. [63].

viruses. One of the optical biosensors is based on the phenomenon of localized superficial plasmon resonance (LSPR), which is suitable for specific detection of different types of analytes. Metal NPs are employed near the fluorophores to increase the fluorophore excitation through the improvement of the electric field. This can affect the radiative decline rate of the excited state of the fluorophore, as well as expose novel non-radiative channels of decay, causing changes in the quantum income [53]. The first paper was based on the quick diagnosis of SARS-CoV-2 by a LSPR sensor activated by the human ACE2 enzyme [54].

Single-walled carbon nanotubes (SWCNTs) have revealed great capabilities for analytical sensing applications [55,56]. Indeed, CNTs inherently emit near-infrared (NIR) fluorescence and can be modified with different sensing agents to progress highly efficient biosensors with quick fluorescence-change data. Compared to common fluorophores, SWCNTs do not have to photobleach, and charitable increases their long-term application. Notably, the NIR emission of SWCNTs is slightly absorbed and spread through molecules, given that data can enter optically obstructed patient testers, thus avoiding the requirement to sample purification restricting the throughput of other viral testing behaviors [56,57]. Researchers developed a biosensor to identify SARS-CoV-2 through developing the innate capability of host proteins to connect virion constituents coupled to a CNT, offering fluorescence readout of the protein acknowledgment events. They employed a protein and SWCNT-based biosensor, which could connect to the spike protein's receptor on the virus. Through a modification approach to immobilize the ACE2 proteins on the surface of the CNTs, they were capable of keeping the fluorescence of the SWCNT. These biosensors were revealed to have an imposing binding ability to the virus spike protein, with a LOD of 12 nM of the spike protein. The nanosensor was less sensitive to viral load in COVID-19 clinical specimens

(typically in the range of 10-10^4 virus copies/microliter), and the nanosensor function can reduce the problem of biofouling affecting the fluorescence response of the sensor. This type of nanosensor could pave the approach for rapid and point-to-point tests to specifically detect SARS-CoV-2 and other common viruses (Fig. 1) [46]

QDs are exceptional fluorescent materials with good optical properties. They show fashionable photochemical properties with the advantages of fluorescence probes in nanosensors over an extensive range of sensors [4,19]. The conjugation methods will aid in preserving the specificity of QD-based biosensing methods. QDs and carbon dots (CDs) have photoluminescence characteristics, which can be applied for labeling pathogenic viruses. The combination of QDs with optical/electrochemical systems would help to increase the sensitivity of biosensors for their use in POCT, including lateral flow immunoassay (LFIA). QD nanobeads (QBs) can be formed through their encapsulation into a polymer, proposing high luminescence characteristics [19]. They can be engaged in the immunochromatographic assay (ICA) as a POCT with the benefits of high speed, which could be applied in the diagnosis of coronavirus from different samples.

One of the rapid types of POCT systems is the LFIA system. A SERS-based LFIA, linking the rapidity and specificity of common LFIA and ELISA assays with surface-enhanced Raman scattering (SERS) readout method, can detect spike RBD protein of virus in 20 min with a LOD of 1 ng mL^{-1} [58]. The RapiRead reader is presently the smallest LFIA system in the world to calculate spike protein receptor-binding domain (S-RBD) antibody levels. RapiRead™ reader can be considered a quick and effective assay to identify neutralizing antibodies [59]. Although the Au NPs-LFIA exhibited various applications in the POCT assay, it has low sensitivity since it is based on the calorimetric method. According to exceptional optical properties, QDs are broadly applied in LFIA systems as fluorescence tags to increase sensitivity. A fluorescent LFIA system using QBs (SiO_2@Au@QBs) was conjugated with S protein. Accordingly, a small sample volume (1 μL) was utilized and the strips comprised two test lines, such as IgG and IgM (Fig. 2). This assay illustrated high sensitivity, several times more than those based on gold NPs. The results demonstrated that a combination of IgM/IgG with SiO_2@Au@QD LFIA could be applied for sensitive recognition of the COVID-19 [60]

The ICA is one of the types of POCT systems with the benefits of low cost, speed, and simple procedure, which has been widely used in medicine. The developments in ICA-based methods for the detection of the respiratory virus enhance the recognition capability of COVID-19/FluA infections. An ICA-based system was developed for the detection of pathogenic viruses with high sensitivity and stability. Nanobeads of QDs were formed through the adsorption of QD multilayers onto the surfaces of SiO_2 with a size of 180 nm. The knowledge of the virus was attained in a short time with a LOD of 5 pg mL^{-1} (Fig. 3). This study exhibited great precision and specificity of this technique with high sensitivity compared to the common AuNP-based ICA assay [61]. A smartphone-based quantum barcode was developed for the monitoring of patients with COVID-19 at different infectious severities. The sensitivity and specificity were 90 and 100% to the virus and more than the results attained from lateral flow assays. This assay permitted the real-time assessment of COVID-19 [62].

The drop-casting assay deposited the graphene oxide (GO) platform onto the Au- fiber Bragg grating (FBG) biosensor. Oxygen-rich functional groups on the surface of GO can be loaded with S glycoprotein onto the surface. Besides, the presence of 2D channels among the stacked GO nanosheets with a spacing of about 0.8 and 1 nm in an environment can improve the exclusive performance of patient saliva. It is similar to a sieve permitting water and another biomolecule to penetrate the membranes. Though, it is resistant to the SARS-CoV-2 with a greater size, which traps them on the surface of the GO layer. Accordingly, viruses trapped on the surface alter the refractive index around the sensor. Fig. 3C shows the development of an Au/ FBG probe decorated with GO to detect the virus through patients' saliva. The probe measured the commonness of positivity in saliva. When the probe was engrossed in patients' saliva, the deviation of light wavelength and intensity from healthy saliva exhibited the presence of the virus. For a patient with high inflammatory, the extreme wavelength shift and intensity changes after 30 min were revealed to be ~1 nm. For a patient in the early infection phase, these values were 0.9 nm. This efficient FBG probe exhibited rapid diagnosis of SARS-CoV-2 in a short time after exposure to patients' saliva [63].

Since the outbreak of COVID-19, strict public health has been employed to prevent the spread of the virus. Although, due to the many regarding the transmissibility and pathogenicity of this virus, the success of these efforts is very restricted. Also, environmental monitoring, especially the analysis and monitoring of the presence of viruses in wastewater are greatly important [64,65]. Although PCR is good in terms of sensitivity and availability, the needs for complex laboratory-based sample management and data processing for a long time are not favorable to the effective observing of samples; there are other types of material besides genetic material in wastewater. On the other hand, other pathogenic microorganisms such as *Escherichia coli, Streptococcus mutans*, and *Bacillus subtilis* in wastewater can impose various stressors on the PCR [66]. Lanthanide metal-doped CNPs (LnCNPs) showed intrinsic advantages according to narrow emission lines and extended lifetimes of lanthanide dopants in the host lattice, which can be applied to the detection of chemical and biological molecules [67,68]. Researchers developed a fluorescence sensor array fabricated from three CNPs, showing effective selectivity toward SARS-CoV-2 detection. By investigating the fluorescence patterns of SARS-CoV-2, influenza and bacteria using LDA, the virus was separated from the other strains with 100% specificity. The detection process was quick in ~15 min with great throughput, and did not require any external needs to washing. This technique could provide continuous data to function as an early diagnosis system allowing municipal communities to yield suitable steps for detecting virus carriers [68].

2.2. Electrochemical/electronic biosensors

Electrochemical techniques, including cyclic voltammetry, electrochemical impedance, and amperometry can offer label-free detection without the need for extra pathways. Researchers reported the electrochemical sensing assay based on surface-functionalized Au NPs, showing promising platforms for the specific detection of coronaviruses. They planned a biosensing electrode with high stability, even under punitive conditions, with a complementary probe that complemented the target sequence [69].

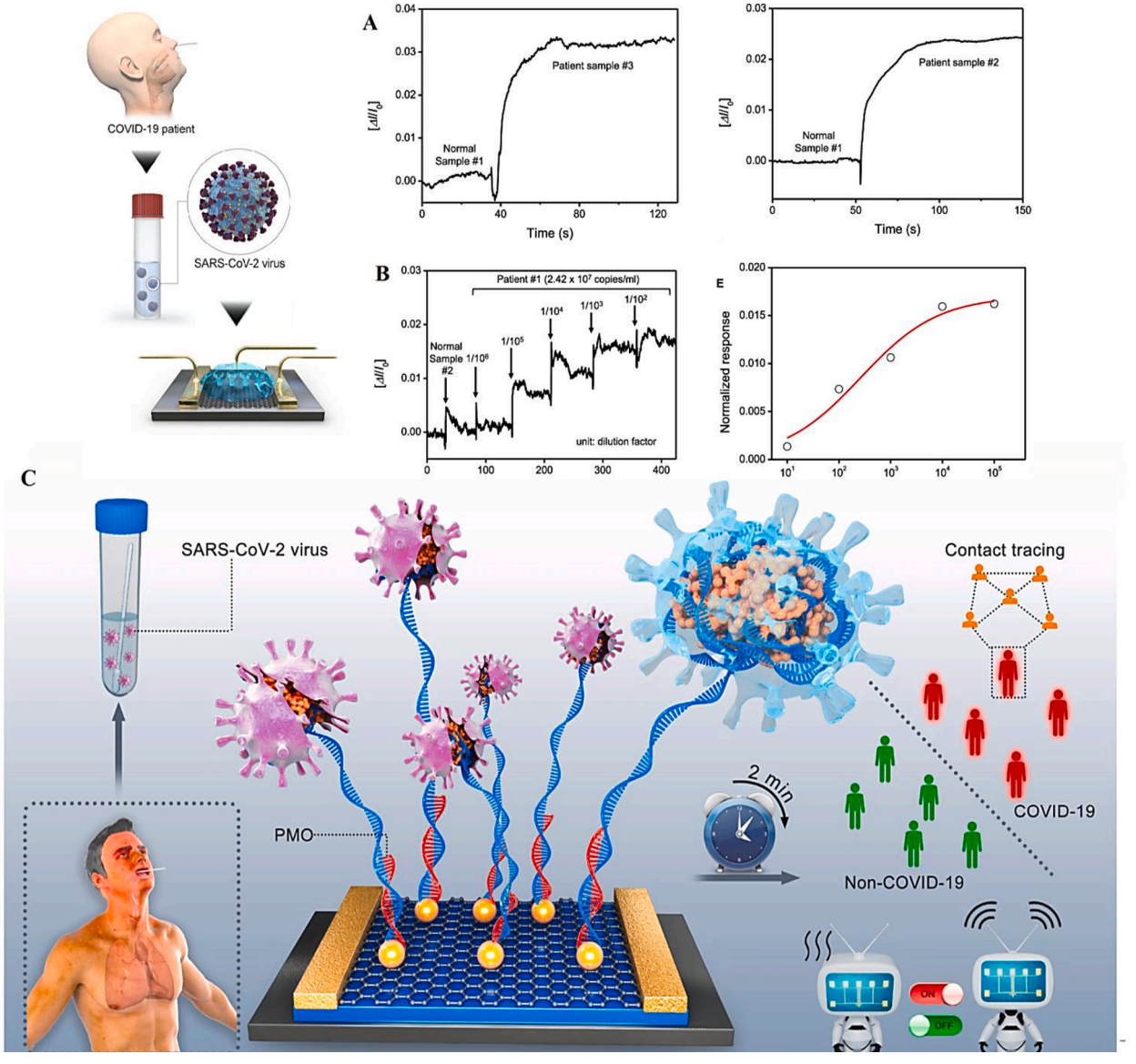


Fig. 4. Sensing of COVID-19 from clinical samples by FET biosensor. (A) Comparison of response signal among normal and patient samples. (B) Response of COVID-19 FET. Reproduced with permission from Ref. [76]. (C) PCR-free detection of virus by using the PMO-functionalized G-FET sensor. Reproduced with permission from Ref. [77].

Electrochemical-based nanosensors have been established based on precise viral RNA and complementary DNA (cDNA) or antigen detection in various samples. Nucleocapsid (N), spike (S), and matrix (M) is mainly antigens applied to recognize coronaviruses. To diagnose SARS-CoV-2, various kinds of electrochemical techniques have been applied [70]. Graphene and its derivatives have been discovered to detect viral pathogens, such as Ebola, Zika, human immunodeficiency virus (HIV), human papillomavirus (HPV), etc. [71]. Graphene and its derivatives have been developed to synthesize a variety of nanosensors according to their outstanding sensing performance, high surface area, and flexibility. Graphene has a great surface area and strong mechanical strength, which is important for manufacturing biosensors [72–74].

Among the various diagnostic electrochemical techniques presently accessible, field-effect transistor (FET)-based sensing shows different benefits, such as the capability to have highly sensitive with low amounts of analytes. FET sensors are deliberated to be possibly beneficial in detection and POC. One of the carbon-based materials for this is graphene owing to its great electronic conductivity [75]. According to these features, researchers developed a graphene-based field-effect transistor (FET) for the diagnosis of COVID-19, which was coated with an antibody against the spike protein [76]. Fig. 4A and B shows the detection potential of the FET sensor using several clinical samples. The COVID-19 FET sensor distinguished between the patient and normal samples. The spike antibody was conjugated on the surface of the graphene. This study described a LOD of 1 fg mL^{-1} of the spike protein and proposed exclusive advantages to biosensing owing to its unique properties, such as great carrier mobility.

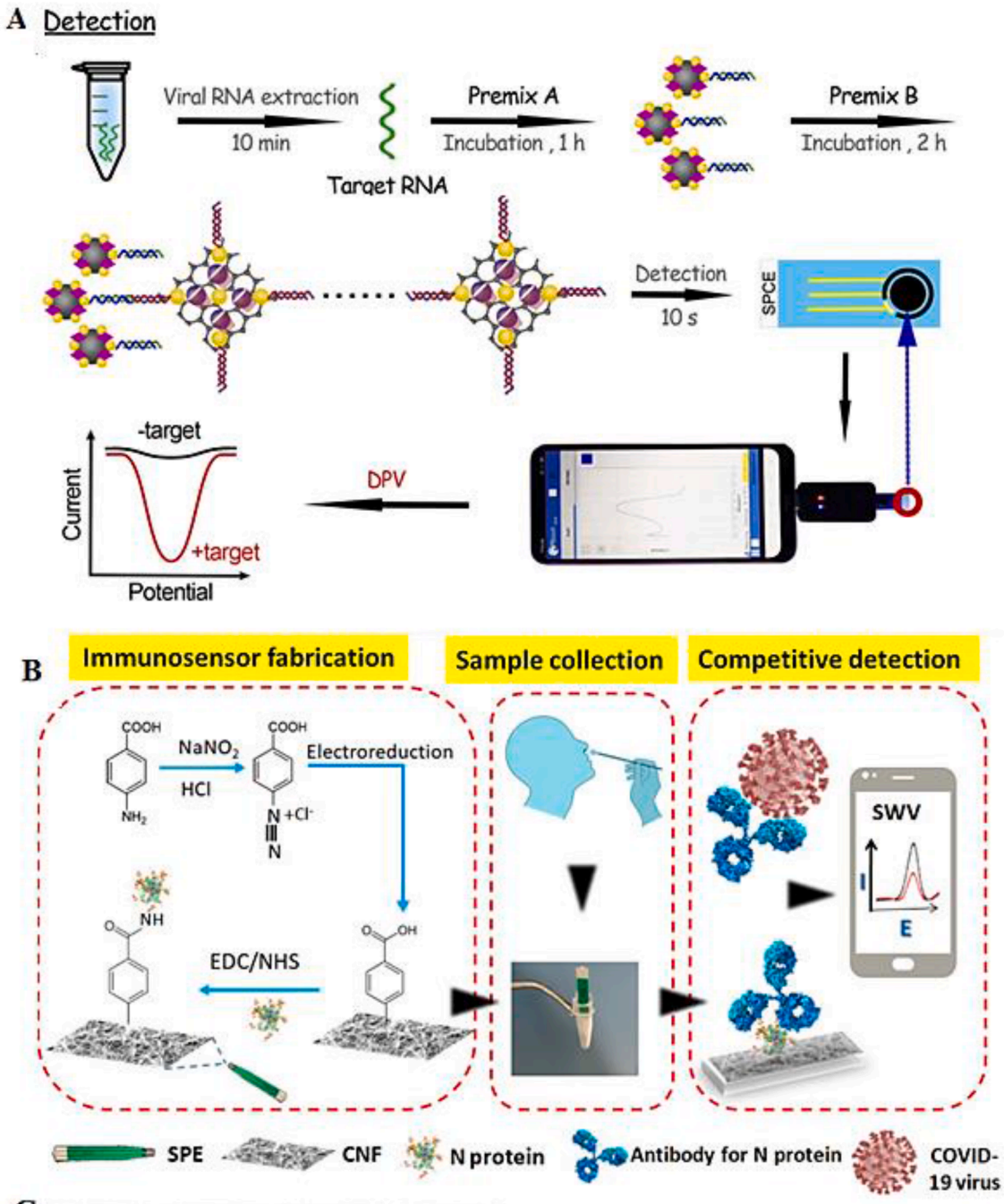
Another diagnostic method is based on rGO-based FET biosensors considered through Au NPs, modified with phosphorodiamidate morpholino oligos (PMO) as a peptide. In this nanobiosensor hybridized with the PMO with RNA-dependent RNA polymerase (RdRp) gene, the biosensor shift could be identified quickly in a short time, without the requirement to amplify. The LOD of detection of this biosensor was about 3.9 fM in serum. In an experiment with 30 clinical samples from the throat swab, the nanosensor showed exceptional precision, with the area under the ROC curve established to be ~0.9. Comparing the biosensor performance of the kappa test with the RT-PCR outcomes, the kappa index was ~0.9, which correlated with the common detection test. This nanoplatform exhibited suitable reusability, proposing the probability of its inexpensiveness. After denaturing the PMO-RNA, it is possible to re-establish the RdRp sequence to the biosensor's surface, and the signal production was similar after the hybridization. This assay could be applied for quick screening apparatus in a sensitive and precise assay, offering a comprehensive testing approach for COVID-19 (Fig. 4C) [77].

Although two-dimensional (2D) FET nanosensors based on graphene have been widely studied, efforts have been made to apply CNT-based properties to FETs. CNT-based FETs are recognized as one of the greatest nanoplatforms for electronic biosensing, with excellent capabilities for the detection of various biomolecules [78,79]. CNT-based FETs were constructed using polymer substrates; the biosensor was prepared by immobilizing the targeted RdRp gene of SARS-CoV-2 on the CNT channel [80]. This nanosensor exhibited a LOD of ~10 fM. However, more explorations are still required to progress this nanosensor, and studies on clinical samples require confirming the diagnosis activity associated with the RT-PCR method.

In addition, the application of these techniques can help to solve various limitations elaborate in manipulative nanosensors, proposing a mixture of great sensitivity without the requirement to amplify viral and with a quick readout time. The formation of ROS is one of the critical side effects of SARS-CoV-2 in lung cells, producing mitochondrial ROS to improve the viral replications [81]. Remarkably, MWCNTs have been applied to design nanosensors for specific recognition of SARS-CoV-2. The study exhibited a COVID-19-induced ROS sensor consisting of MWCNTs grown on the needles to synthesize three electrodes. Indeed, the calibration curve of ROS sputum levels was generated, which was related to a certain diagnostic range. The detection range of negative, suspected, and positive COVID-19 was less than 190 μA, between 190 and 230 μA, and more than 230 μA current peaks, respectively. The results exhibited ~97% sensitivity and 91% specificity after evaluation of clinical samples. One of the major advantages of this biosensor is its capability to provide a quick screening apparatus to assess the health of people supposed to be infected in less than 1 min [82]. At this point, an electrochemical ROS detector in the sputum sample was applied for the diagnosis of patients who might be doubtful of the virus.

Different commercial POCT devices are broadly developed to diagnose proteins based on antigen-antibody. Though, one of the limitations of using POCT devices is the lack of signal amplification, preventing their use in early clinical diagnosis. Thus, the nucleic acid testing (NAT) technique based on signal amplification can identify nucleic acids [83]. This assay contains different PCR, loop-mediated isothermal amplification (LAMP) reactions, and recombinase polymerase amplification (RPA) [84]. The combination of MWCNTs with rGO shows good thermal and electrical conductivity, which has been applied in electrothermal heaters and biosensors since rGO can be considered as an increased conductive dispersant when combined with CNTs. The paper-based analytical system (named HiPAD) integrated with an rGO/MWCNTs heater to diagnose the virus by LAMP reaction was developed accordingly [85]. HiPAD can be detected viruses with a range from 2.5×10^{10} copies mL^{-1}. Furthermore, with small modifications, the HiPAD could be simply stretched to M-HiPAD for multiplex detection. Indeed, the HiPAD was suitable for POCT. Notably, by applying HiPAD the main limitations could be solved in the diagnostics field by diminishing and integrating a cost-effective heater into a POCT. This novel HiPAD could be combined with rGO/MWCNTs heaters, showing high potential in POCT with low cost, especially for the undeveloped areas [86].

A super sandwich-based electrochemical biosensor with high sensitivity includes a target, label probe (LP), capture probe (CP) and secondary probe. The 5′ and 3′ of the target are complementary to CP and LP. Consequently, sequence detection can be attained through probes, CP, and LP hybridize [87,88]. An electrochemical nanosensor based on a super sandwich method was designed using sulfocalixarene (SCX8)-functionalized rGO decorated with the capture probe CP and Au@Fe_3O_4 nanocomposites (~388 nm), showing high efficiency to target the RNA of virus. The design of a super sandwich-type biosensor was performed by labeling of CPs with thiol immobilized on the surfaces of Au@Fe_3O_4, immobilizing SCX8-TB on RGO, designing a sandwich structure of "CP target-LP", and using AP as a concatamers forming agent [85]. Fig. 5A shows the detection of SARS-CoV-2 on the ORF1ab gene, which premix A and target



(caption on next page)

Fig. 5. (A) Electrochemical biosensor using a smartphone based on a super sandwich method for the virus. Reproduced with permission from Ref. [85]. (B) The cotton- electrochemical immunosensor for SARS-CoV-2 detection; includes sample collection; functionalization of the CNF Electrode, and detection using competitive and SWV technique (C) (I) SEM images of the carbon electrodes and (II) the carbon electrode/CNF. Reproduced with permission from Ref. [89].

samples were gestated at RT condition, and then incubated with premix B for 2 h. The electrochemical signal of TB was detectable in a short time through the smartphone. Thus, the method was simple and rapid, and the detection of the target with a LOD of 3 aM could be obtained. Besides, this method can be applied in various samples such as plasma, throat swabs, urine, and serum. Compared to RT-PCR, this nanosensor acted greater in sensing respiratory samples with high accuracy and better performance. The LOD of RNA detection using this technique was ~200 copies mL^{-1}, which is greater than the RT PCR with LOD of 50–100 copies mL^{-1}. Thus, by applying electrochemical detection, this POC technique can be employed without the requirement for high-cost apparatus .

Carbon nanofibers (CNFs) are one of the carbon-based nanomaterials with high potential in designing biosensors owing to their stability and high surface area. There is similar conductivity and stability between CNFs and CNTs. However, one of the main characteristics of CNFs is the accumulation of graphene plates, creating more edge locations on the outer wall of CNFs for electron transfer. CNFs with these properties can be considered as attractive candidates for electrode materials. The colorimetric assay was attained based on the discernment of the color change, acting as rapid and simple technique. The electrochemical immunosensor was established by immobilizing the virus N protein after the modification of CNF-printed electrodes. The carbon electrode displayed a graphitic construction, although the CNF electrodes showed a greater surface area of the electrodes (Fig. 5C). The LOD of this sensor was 0.8 pg mL^{-1} to the virus, representing high sensitivity for the nanosensor. Cross-reactivity of the electrochemical nanosensor was performed in the presence of other virus antigens, including influenza A and human coronavirus, showing high selectivity (~90%) in spiked nasal samples (Fig. 5) [89].

Graphite-based nanomaterials (GNs) containing various stacked graphene sheets have shown homogenous spherical shape with excellent conductivity to biomolecular conjugation [90]. These spherical types of nanomaterials with a size of ~4 nm comprise ~10 graphene sheets. These graphite-based nanomaterials show high conductivity according to the graphene-like properties and offer a great surface area for enzyme immobilization. Furthermore, the sensor electrode deposited with GNs increases electrode surface area more than the glassy carbon electrode and eases fast electron transfer to the working electrode. The cDNA-modified Au@CD NPs were developed on the coated paper electrode for the RdRP detection. The deposited GNC film on the paper permitted the expansion of a voltammetric genosensor by increasing the electrical conductivity of the substrate and enhancing the effective electrode surface. With enhancing the RdRP concentration, the peak of TB increased to a LOD of 12.00 nM. This biosensor exhibited good selectivity with high stability to spiked sputum samples [91].

2.3. Microfluidic technology

Microfluidics technology shows systems that control small volumes of fluids. This technology integrates tools to handle small volumes of fluids to control biological and chemical procedures. The study on microfluidics devices has been developed for 15 years, but its use in the biomedical field recently gained significant attentions. Such systems have been called the “Lab-on-a-chip” [92]. Recently, microfluidics technology and nanotechnology have been combined with advancements in diagnostic systems. The growth of some nanomaterials such as CNTs on the surfaces of microfluidic systems permits the formation of small microfluidic systems, leading to a reduction of analysis processes conducted on a laboratory bench. These materials display unique properties regarding the electrical conductance, strength, thermal stability, and optical properties, affecting the sensitivity of a system for the detection of viral infections [93]. Researchers have developed Au/Ag coated CNTs integrated with SERS, thus effectively recognizing pathogenic viruses from different samples. The system applied size-dependent trapping of SARS-CoV-2 through their Raman signature. The device acted in a short time. Based on the application of nanofilters or CNTs on polydimethylsiloxane (PDMS), the system could be organized into two models [94]. Long COVID-19 management can be programmed using advanced technologies based on point-of-care testing and biosensors, including LFIA techniques or microfluidic biosensors [95].

2.4. COVID-19 prevention

One of the main strategies to inhibit COVID-19 is to use protective apparatus such as gloves, face masks, and face shields that can be applied as a barrier against viral pathogens. However, the lack of global personal protective equipment (PPE) supply has forced many people to reprocess their apparatus, which is similar to being unsafe. Nanotechnology can help to solve this problem by modifying PPE levels not only to absorb and inactivate viruses but also to be recyclable and washable without cooperating efficacy and safety. Carbon-based nanomaterials show a major role in this regard. Investigations are being directed to the utilization of masks after decontamination through a microwave irradiation [96]. Graphene and its derivatives have exclusive properties for the modification of masks owing to their superb hydrophobicity, increasing the wetting resistance of masks and improving the self-cleaning of them; these materials exhibited good electrothermal activity for inactivation of the pathogens [97]. Some of the carbon-based nanomaterials(such as CNTs) can be coated on the surface of polypropylene (PP) masks to increase their self-sterilization capability of them [98]. Fig. 6 displays the effects and unique properties of carbon-based nanomaterials, causing them to be prospective applicants for producing PPEs against COVID-19.

Till now, several advancements have been developed in the formation of graphene-based (nano)materials, CNTs and their

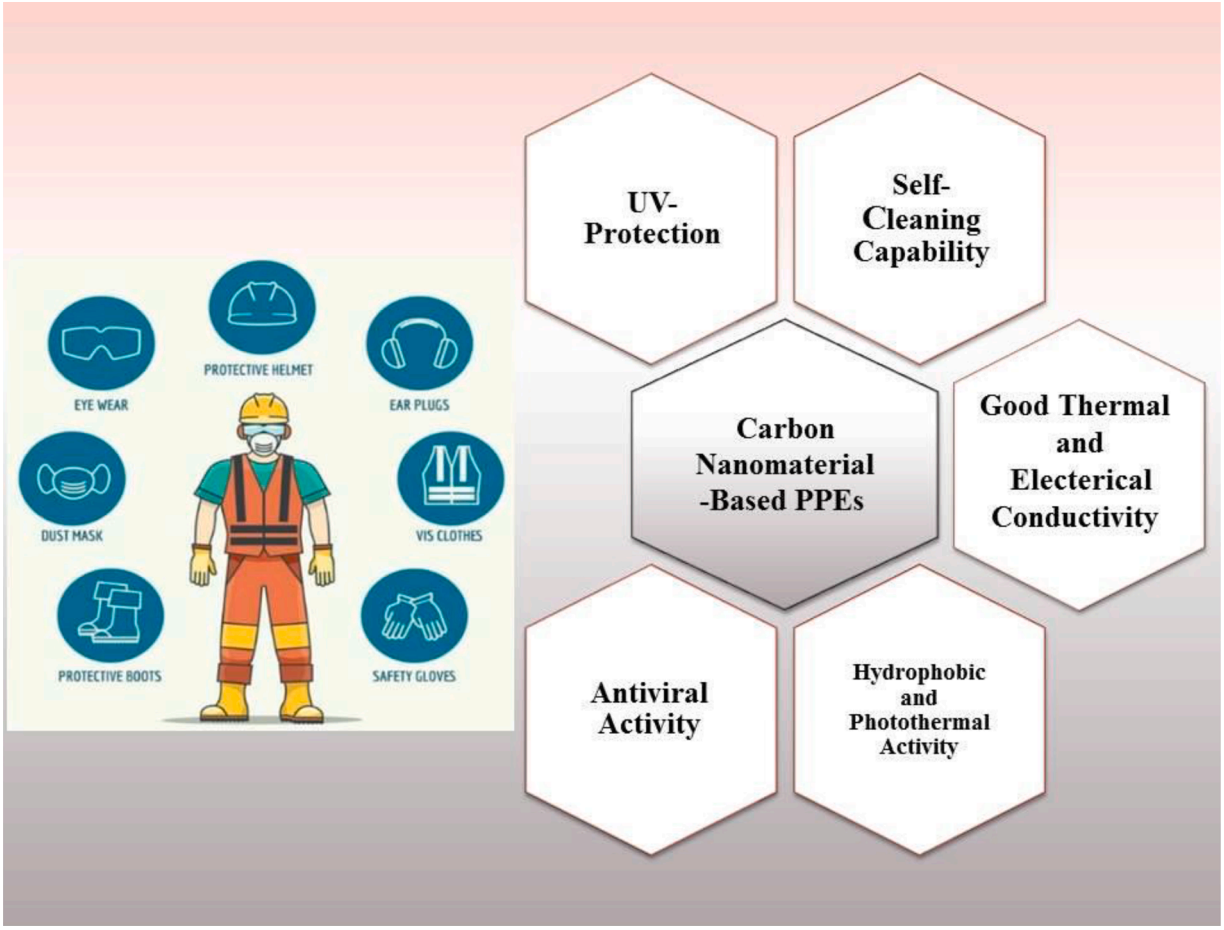


Fig. 6. Schematic illustration of the fascinating properties of carbon-based nanomaterials in PPEs against SARS-CoV-2.

derivatives to battle SARS-CoV-2:

1. Development of a mask with hydrophobicity performance, usability for a long time, and reusability after solar illumination. This mask is comprised of graphene nanosheet and carbon film to offer safety from SARS-CoV-2. Through the electron cyclotron resonance sputtering assay, the deposition of the film on a Si substrate was performed. These masks display good performance compared to laser-induced graphene coatings (Fig. 7A) [99].

2. Development of temperature-sensitive commercial and self-cleaning recyclable masks using laser preparation assay and graphene. These masks exhibited a unique procedure to functionalize masks with excellent photothermal and self-cleaning properties. According to its photothermal activity, laser-induced graphene can be applied as antibacterial coatings. Due to its outstanding photothermal activity, the graphene coating displayed ~99% greater bactericidal activity in *E. coli* [100]. These materials improve the ability to self-cleaning. Through the creation of superhydrophobic coatings, enhanced protection from respiratory droplets could be delivered. When the mask is exposed to sunlight, the temperature of the mask could rise to 80 °C, disturbing the pathogenic viruses (Fig. 7C) [101].

3. Development of masks with bright self-sterilizing properties; an interdigital electrode was ready through binding a conductive tape to a filter layer formed of melt-blown fabrics, then covering a layer of graphene due to the good thermal/electrical properties. The graphene-modified fabric can produce great amounts of heat to reach 90 °C, providing suitable platforms to sterilize the viruses binding to the filter layer (Fig. 7B) [102].

4. The spray-coated SWCNTs on surgical masks made of melt-blown PP increase their antibacterial and antiviral properties. The presence of SWCNTs could increase the hydrophobic properties of the mask. By being exposed to sunlight for a short time, the coated mask exhibited good photothermal activity, improving the surface temperature of the mask to more than 90 °C. This temperature was enough to abolish different pathogens [98].

5. The synthesized coronavirus filters with the structures of calcium carbonate/ethylene glycol/cellulose/polyethylene/activated carbon could inhibit coronaviruses, with the efficiency of ~80, 95 and 100% for particles size 50–200 nm. The outcomes exhibited the decreasing size of the holes through nanomaterials in the filter to 30 nm. These carbon-based materials showed that the activated carbon NPs have a good potential to be applied for mask fabrication [103].

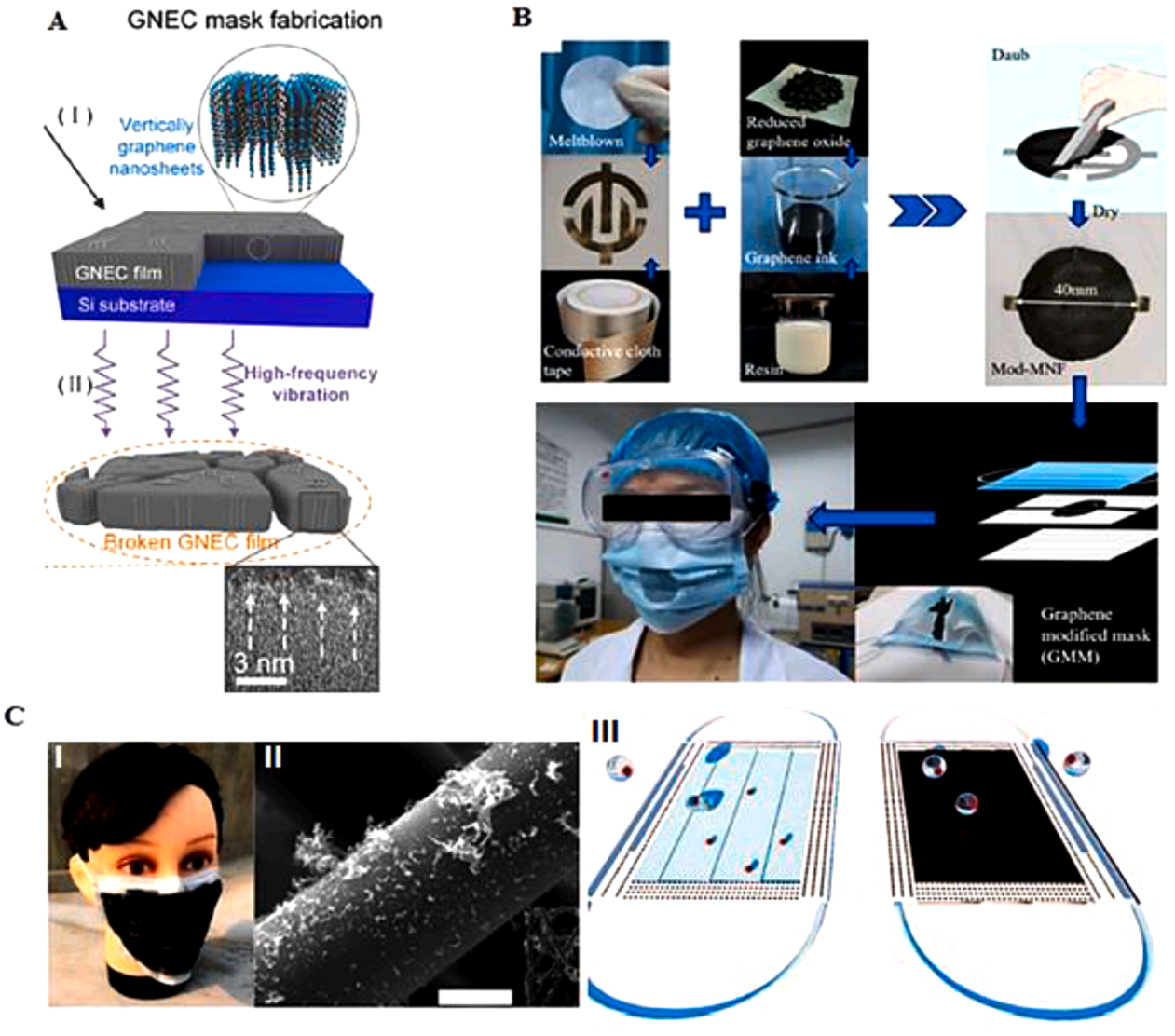


Fig. 7. The role of carbon nanomaterials in the production of Personal Protective Equipment (PPE). (A) Construction procedure of the GNEC mask. (I) The deposited GNEC film with graphene nanosheets. (II) GNEC film was destroyed through a vibration. Reproduced with permission from Ref. [99]. (B) Schematic shows the mod-MNF and GMM construction procedure. Reproduced with permission from Ref. [102]. (C) (I) The laser-made-up graphene mask. (II) The graphene-coated fiber inside the mask. (III) The self-cleaning of the graphene-coated mask (right), then the blue mask (left). Reproduced with permission from Ref. [101].

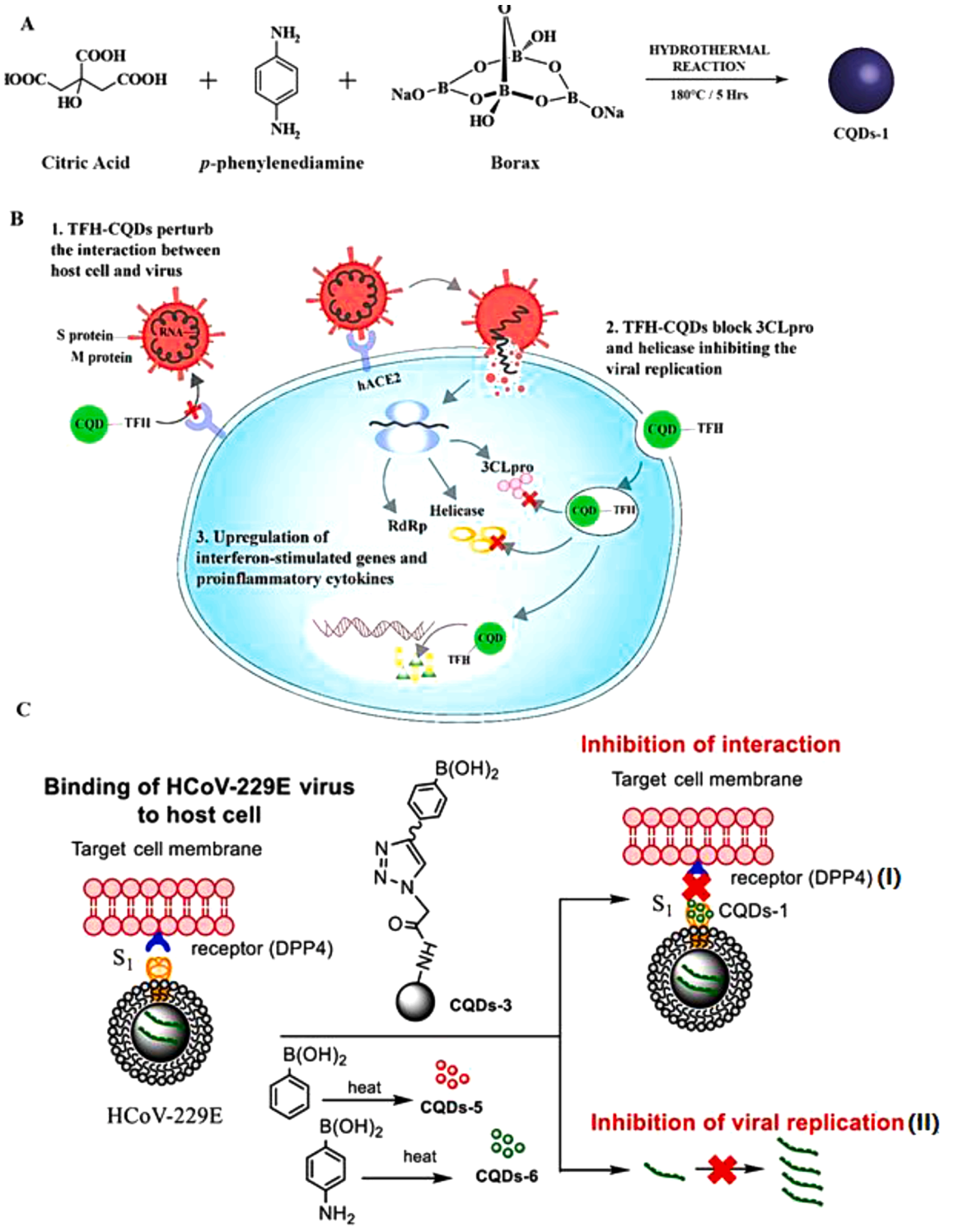


Fig. 8. (A) The hydrothermal assay of heteroatom co-doped CQDs-1 from citric acid. Mechanism of activity of TFH—CQDs against COVID-19. (B) The role of triazole-modified heteroatom (TFH)–CQDs activity against COVID-19. Reproduced with permission from Ref. [111]. (C) The effect of CQDs on connecting human coronaviruses (HCoV)−229E virus to cells (I, II). Reproduced with permission from Ref. [115].

6. Polyacrylonitrile/GO air filter was developed for removing the particulate matter 2.5 μm from indoor with an efficiency of 99%. This filter has a high potential for preparation in large-scale production for use in air filtration media. These filters can remove particulate matter r2.5 from indoors and yield a cleaner air [104].

7. The fabrication of an air filter based on graphene for the preparation 3D- mask for SARS-CoV-2. Indeed, modified graphene's are a virtuous candidate for air filters according to its excellent properties, antiviral activity, and great compatibility. Besides, modified graphene with nano construction and negative charge can offer an antiviral activity for the inactivation of the virus. SARS-CoV-2 has a positive charge, which can be adsorbed to the graphene *via* redox reaction and electrostatic interactions. Thus, the adsorbed virus on the graphene surface can be washed off. This filter exhibited 98% filtration efficacy. The role of modified graphene-based filters in the management of long COVID-19 has different mechanisms, such as sharp edge insertion and oxidative stress according to the imbalance of oxidation/antioxidation and graphene materials interfering with virus metabolism [105].

8. CNTs are virtuous materials to the formation of nano-fiber filters. This filter synthesized from CNTs maintained through porous polyester for improvement the filtration efficiency. The air filter displayed 99.9% filtration efficiency in a short time. This air filter with electrically conductive properties could be heated to 130 °C for inactivation of virus on their surfaces such as beta coronavirus (MHV-A59) [106].

3. Carbon-based nanomaterials against COVID-19: therapeutic potential and inhibition

3.1. Inhibitory applications

The advance of vaccines/drugs to battle coronavirus infections needs comprehensive studies with special focus on mechanisms associated with the virus. Also, it is important to specifically detect viral proteins and antigens for targeted inhibition. The role of carbon-based nanomaterials in preventing viral replication has been reported in several studies. Researchers reported that GO could inhibit viral infection by conflicting to virus-cell binding [107]. In addition, the surface-modified carbon nanodots could act as entry inhibitors by contact with the virus [108]. Besides, CDs might prevent viral replication through adaptable type I interferon response.

CDs have special attention owing to their outstanding cell membrane permeability and biocompatibility. These nanomaterials with a size of less than 10 nm can be applied for inhibition of SARS-CoV-2 [109]. They can be deployed in different fields such as bio-imaging, drug delivery, optical sensing, etc. [110]. Cationic CDs exhibited suitable antiviral activity, preventing the proliferation of porcine epidemic diarrhea virus by changing the surface protein. Besides, they inhibit the generation of negative-strand RNA and prevent the increase of ROS through the virus [19]. Fig. 8A shows the antiviral inhibitory effects of CDs made from 4-aminophenylboronic acid against COVID-19. The results exhibited inhibition of the viral entry, which was attributed to the interaction of the functional groups of carbon nanomaterials with the viral entry receptor DPP4 [111].

CQDs with high biocompatibility and low toxicity can be considered promising candidates in bio- and nanomedicine. The nanomaterials synthesized through green carbon resources showed both fluorescent features and bioactivities such as antioxidant, anticancer and anti-inflammatory effects [112,113]. Alternatively, limited studies were reported with an exploration of the antiviral activity of CQDs. the therapeutic effects of 5 μg mL^{-1} of EDA-CQDs or EPA-CQD on human noroviruses were reported, showing the effective antiviral activity by inhibition of viral-like particles (VLPs) connecting to histo-blood group antigens (HBGA) receptors on human cells [114].

Triazole derivatives can be applied as an inhibitor of coronaviruses, causing the blockage of viral enzymes. CQDs were deployed as inhibitors by blocking viral entry. Triazole-modified heteroatom co-doped CQDs (TFH—CQDs) could block viral entry through disturbing different interactions with the target cells. These nanomaterials exhibited vital roles in enhancing the expression of inflammatory factors. Thus, CQDs could perform important potential in enhancing the expression of inflammatory cytokines against HCoV-229E (Fig. 8C) [115].

Graphene, as a 2D material, is a favorable material to progress virus inhibitors owing to the simplified multivalent interactions [116]. Functionalized graphene tends to inhibition of different viruses according to their great binding affinity. Besides, graphene-based nanomaterials can capture the viruses through after functionalization with suitable antibodies or ligands, offering promising systems for trapping and electrostatic interactions. In addition, graphene sheets can destroy the viruses through hydrophobic interactions [117]. The antiviral activity of GO/rGO can be credited to the exclusive single-layer structure and negative charge [8,118]. Graphene can abolish the virus surface proteins. It was described that the sharp edges of the nanosheet could inactivate the virus through disturbance of their structures, causing the discharge of intracellular metabolites.

GO sheets can interact with virus spike and the ACE2-bound spike complex, showing more intensely with the spike or ACE2. GO sheets can be decreased copies to three various viral clades. The results demonstrated that GO sheets had the capability to interact with viruses and disturb them in the presence of mutations on the spike of virus [119]. Graphene sheets with long alkyl chains have high antiviral potential against COVID-19 without high toxicity in contrast to different cell lines. Graphene acted as suitable platforms to permit the interaction of the negatively charged polyglycerol sulfate (PGS) branches with the virus particles by positively charges. Thus, this platform exhibited the highest antiviral activity against COVID-19 (BetaCoV) (Fig. 9) [117]. Besides, the results of cell viability tests on the lung epithelial cells (A549) demonstrated that a platform with shorter aliphatic chains (<10) did not display important toxicity. In general, the modified graphene-based nanomaterials could prevent the infection of enveloped viruses, paving a way for novel therapeutic ways towards COVID-19 and other viral infections.

Fullerene has suitable antioxidant and antiviral properties, with excellent hydrophobicity properties; antiviral fullerene derivatives can be formed to form hydrophilic drugs [120]. Several explorations have been conducted on the role of fullerenes with antiviral properties. The first report of using fullerenes as antiviral agents dates back to 1993, which showed that fullerene has anti-HIV activity

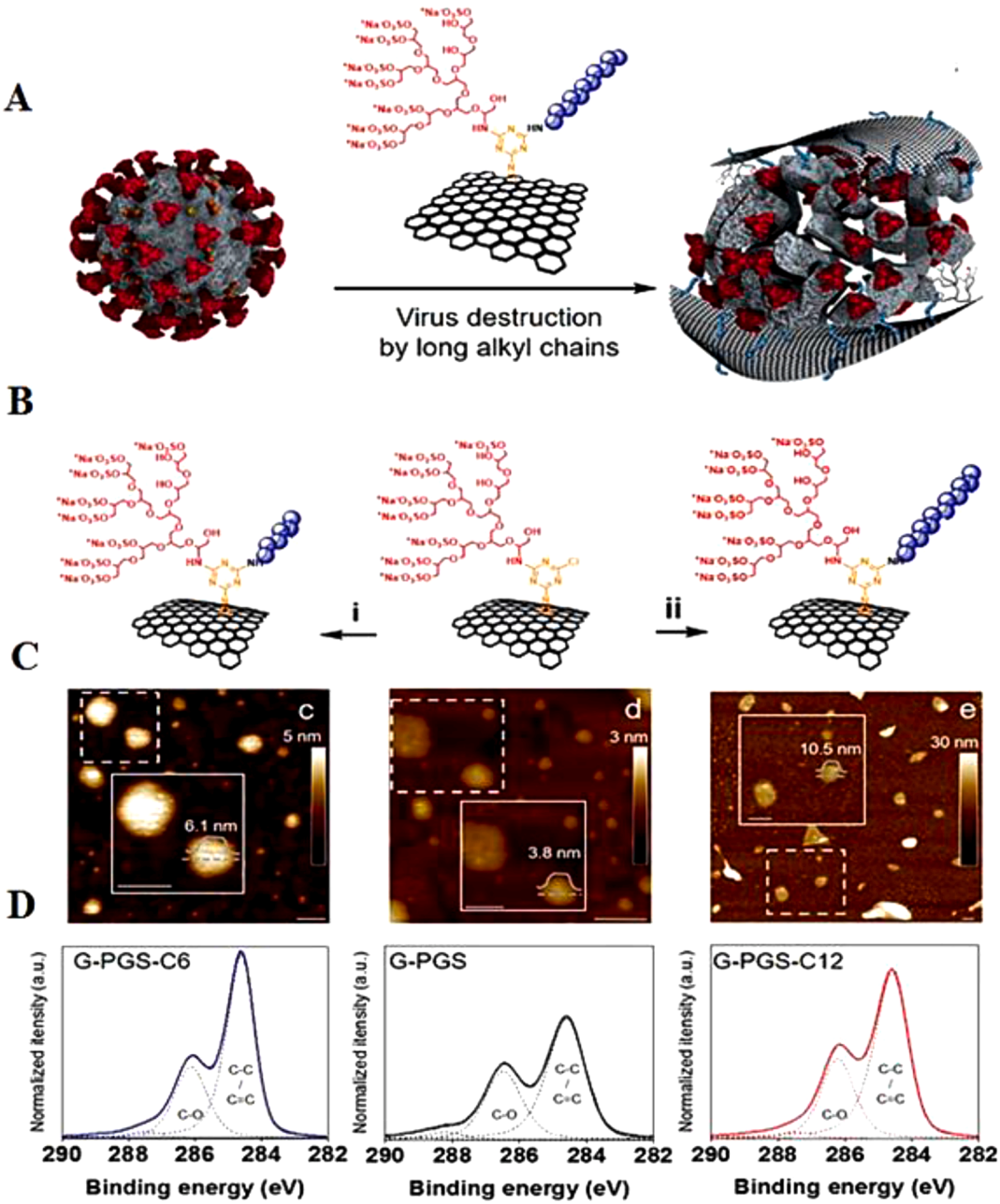


Fig. 9. (A) The interactions among G-PGS-C11 and virus. (B) The synthesis of G-PGS-C*x*. (C) AFM images of graphene sheets and (D) XPS spectra to G-PGS-C6, G-PGS, and G-PGS-C12, respectively. Reproduced with permission from Ref. [117]. Copyright 2021 Wiley-VCH GmbH (CC BY).

by blocking encoded enzymes since fullerenes could be located at active sites of the HIV protease [121]. Different antiviral activities have been detected owing to the easy to functionalization of fullerene. In one study, researchers exhibited that a bis(monosuccinimide) derivative of p,p′-bis(2-aminoethyl)-diphenyl-C60 prevented HIV-1/2 in human lymphocytes [122]. Thus, fullerene derivatives with suitable anti-HIV activities can be applied for the treatment of COVID-19.

One of the important limitations is the low solubility of fullerenes in water, showing a robust restriction to their applications in the medicine [123,124]. Thus, the preparation of fullerene solution derivatives is demanded antiviral activity, especially against SARS-CoV-2. Kornev et al. developed a water-soluble fullerene derivative (50–100 mg mL^{-1}) using chlorofullerene, and $C_{60}Cl_6$, as a precursor substrate, showing high anti-HIV activity with low cytotoxicity. Also, several studies have been planned on the antiviral activity of another fullerene C70 derivative. Compared to C60, the synthesis of water-soluble derivatives of C70 is an important challenge due to less symmetry. However, Kornev et al. developed greatly soluble C70 compounds, which had low antiviral activity

Table 2
Some selected examples of inhibitory potential of carbon-based nanomaterials against COVID-19.

Carbon Nanomaterials	Mechanism of viral inhibition	Size	Properties	Refs.
CDs/CQDs	Inhibit viral entry Inhibit viral replication	2–6 nm	Biocompatibility Nontoxicity Cell membrane permeability Surface functional groups	[108,115, 131]
Graphene/GO/rGO	Destroy the viruses through hydrophobic interactions/ physical disruption Capture the viruses Electrostatic trapping	1–10 nm	Large surface area Have higher negative charge Low toxicity	[132,8]
Fullerenes	Inhibit viral entry Inhibit viral replication inhibitor of viral activity or as a photo-activator	2–3 nm	Antioxidant/ antiviral properties High hydrophobicity properties	[133]
CNTs	Virus inactivation/capture Able to create reactive oxygen species (ROS)	SWCNTs: 0.4–2 nm MWCNTs: 10–100 nm	Higher surface area Flexibility High mechanical strength Resistant to most acids and bases	[21,134]

and low cytotoxicity for H3N3, one of the types of influenza virus. In addition, the antiviral activity could be detected through the interaction of C70 derivatives with the gp120 envelope protein of HIV-1[125].

One another challenge related to the fullerene derivatives is the toxicity evaluation of fullerene. Low cytotoxicity was reported from fullerene; however, more explorations are still required, especially regarding C_{60} derivative isomers. In one study, malonic acid/ fullerene with high inhibitory activity against SARS-CoV-2 exhibited nontoxicity to HeLa cells (64 mM) [126,127]. In addition to the application of CNTs in the progress of biosensors, they have also been used to capture and inactivate viruses. CNT-based filters were developed to remove viral and different pathogens. CNTs can possibly be applied to the treatment of different pathogenic viruses, including influenza, dengue virus, HIV, and coronaviruses [128]. The potential of MWCNT for the removal and inactivation of viruses from contaminated water by MWCNT hybrid membranes was reported. Studies showed the interaction energy among the CNTs and B domain in SARS-CoV-2. SWCNTs exhibited an affinity to the spike glycoprotein. The adsorption of CNTs on the B domain managed the major change in solvent-available surface and hydrogen, offering an evenhanded assay to inhibit the interaction among the ACE2 [129].

ROS-based strategies can be applied for destroying different pathogenic viruses, especially coronaviruses. Inactivation of the virus can be performed by the capture of ROS on the CNT surfaces loaded with the metal NPs. Indeed, the functionalization of SWCNTs with metals can destroy the virus, as well as increase the interactions among the sensing material and the molecule according to their high catalytic activity [11]. For instance, metal decorated SWCNTs were assessed for hydrogen peroxide (H_2O_2) adsorption for viral inactivation. They engaged first approaches based on the density functional theory (DFT) to study the capture of H_2O_2 on SWCNTs and metal decorated SWCNTs. H_2O_2 on pristine SWCNT showed very poor physical adsorption but functionalized SWCNT with metals as adsorbents showed a large improvement in energy absorption. It was revealed that Ru and Rh-SWCNT nanoplatforms with exceptional activity in H_2O_2 adsorption. Besides, Pt/Cu-decorated SWNCT-H_2O_2 platform displayed great potential for inactivation of viruses with a long shelf-life (2×10^{12} years); they are excellent platforms for planning highly efficient apparatus against COVID-19 [11].

One of the newest topics in COVID-19 prevention is three-dimensional (3D) printing of protection equipment that can disable the virus. Due to the spread of the coronavirus and the persistence of the virus to date, chemical disinfectants, although widely used to kill pathogens, are still harmful. So far, many studies have focused on the role of nanotechnology in dealing with COVID-19 emergencies (Table 2). A new study exhibited the photocatalytic activity of graphene NPs inserted in the broadly applied 3D-printable polylactic acid (PLA). The most significant properties that distinguish graphene from various nanomaterials, along with optical properties, are the interaction of graphene and various types of pathogens. Using NIR (808 nm) makes it possible to kill a virus on surfaces by the light of sunlight. Given that exposure to light can be a way to sterilize the surfaces of substances; these outcomes permit the widespread use of graphene PLA filaments. The use of PLA-G-based systems can be very wide and even beyond hospital settings. In addition, COVID-19 3D printing can be applied to design the suitable platforms with antiviral effects. Indeed, by improving the mechanical properties along with the probability of sterilizing the surface through NIR can eliminate the need to reduce gypsum and casting in emergencies (Fig. 10) [130].

3.2. Drug and vaccine delivery

Nanotechnology can be applied for targeted antiviral drug release, thus developing smart vectors with reduced side effects of drugs. However, several antiviral drugs can damage the normal cells and cause other damaging side effects with a great dose. This approach also addresses a subject rising from the lower water solubility of antiviral drug prevention problems to smart delivery systems. Recently, in one study, carbon-based nanomaterials exhibited promising potentials for targeted delivery of antiviral drugs. Their size and surface properties make them appropriate candidates to be encapsulated and loaded with various antiviral drugs. Though many antiviral drugs are presently introduced to treat SARS-CoV-2, carbon-based nanomaterials can be applied for reduce their possible side

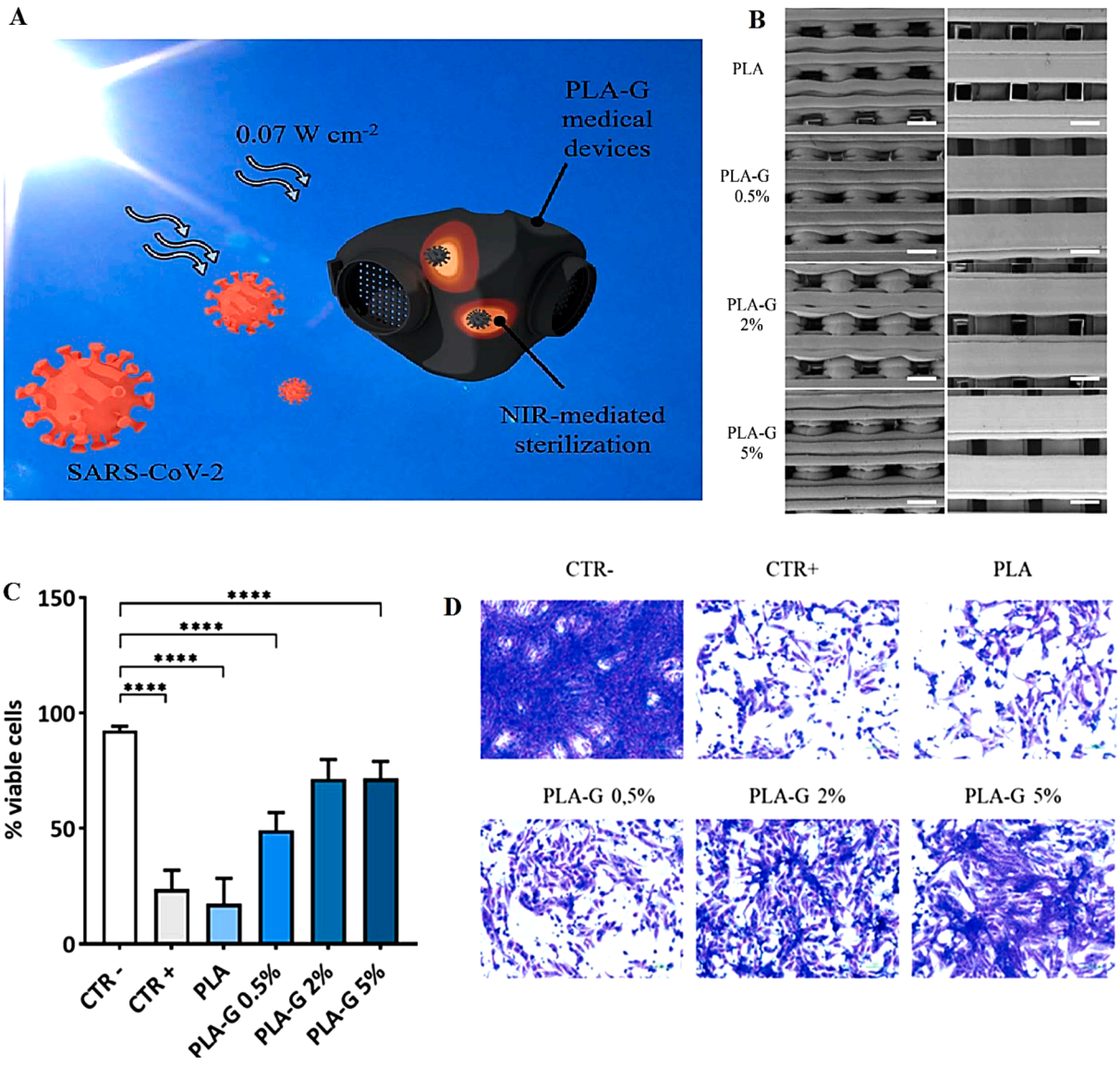


Fig. 10. (A) 3D-printed graphene PLA-G devices against SARS-CoV-2. (B) Properties of 3D printed structures through SEM. (C-D) Graphene/ PLA decreased infectivity of SARS-CoV-2. Exposure of virus-containing solution, at the concentration of PLA-G with 0.5%, meaningfully decreased viral infectivity in VERO cells. Reproduced with permission from Ref. [130].

effects and improve targeting properties. Notably, nanomaterials show similar size to coronaviruses (~50–140 nm), and they can be considered for the inhibition of these viruses, showing efficient therapeutic results with high loading capacity for antiviral drugs.

Most recently, remdesivir has been known as a significant drug against SARS-CoV-2. Carbon nanomaterials (*e.g.,* CNTs) were deliberated in developing new drug delivery carriers, and the interaction among CNTs through carboxylic group and Si-doped CNTs with remdesivir drug were considered by density functional theory (DFT). The outcomes displayed that the Si-doped CNTs as good delivery platforms for remdesivir owing to their improved thermodynamic properties [135]. The modification of CNTs through the covalent and non-covalent functionalization and doping of different factors onto CNTs, such as boron, nitrogen, sulfur, can help them for overcoming their limitations such as solubility and reduced toxicity in drug delivery systems (DDSs). Despite the obvious advantages of high-cost experimental techniques, the computational studies with the goals of the study of the mechanism of the interactions among CNTs and drugs have been deliberated due to the high cost of the experimental methods [136,137].

GO-based systems with the accidental distribution of the oxygenated functional groups can be used as anti-pathogens and in DDSs. Graphene and GO-based nanomaterials have been widely applied to manipulative targeted and stimuli-responsive DDSs by an external stimulus (temperature, light, ultrasound, and magnetic field) or internal stimuli such as pH can be applied for targted drug delivery with greater bioactivity and good temporal/spatial control. Consequently, modified graphene-based nanomaterials have shown

suitable applicability for manipulating smart DDSs [138]. However, the toxicity of GO is the main challenge; the tunability of the size can lead to the nanomaterials being compatible.

GO QDs with low toxicity have shown suitable applicability in biomedicine as DDSs. GO QDs show a single atom layered structure ranging from 1 to 20 nm [139]. Researchers evaluated several GQDs with various surface modifications and sizes for their toxicity (*in vivo* and *in vitro*). Accordingly, GQDs modified with amine and carboxyl groups displayed less toxicity than GO and rGO; these nanomaterials with biocompatibility can be considered as promising candidates for DDSs.

In addition, GO QDs in smaller size professionally decrease ROS as well as cell toxicity, and prevent neurotoxicity by metabolic regulation [140]. Carmofur act as an antiviral drug, preventing viral replication in cells (EC50 = 24.30 μM). It was utilized as chief compound to progress antiviral treatment against COVID-19 [141,142]. GO QDs loaded with carmofur can be formed into a protease binding site (M_{pro}), which is active in drug entry into the catalytic site. Indeed, the results illustrated that GO QDs could act as efficient nanocarriers for targeted delivery of drug inhibitors. These outcomes proposed that the binding pocket of M_{pro} was not constant throughout the interaction with the Carmofur/GOQDs. The results provided visions into the use of GO QDs as a high efficient carmofur delivery system to treat patients with COVID-19 [142].

Graphene exhibited outstanding drug loading capability according to its π-π conjugation at every graphene layer, which can proficiently adsorb macromolecular drugs and offers an efficient delivery system to nucleic acid/ protein delivery. Its stable structure and chemical properties significantly restrict the delivery of drugs, and these properties make drugs incapable of reaching therapeutic activity. Researchers developed an effective vaccine against SARS-CoV-2 through a carnosine GO loaded with the CpG and protein antigen (RBD) [143]. Different studies demonstrated that CpG oligodeoxynucleotide had the stimulatory effects towards the body's immune system, and CpG oligodeoxynucleotide is a hopeful adjuvant [140]. The construction of neutralizing antibodies was established after the vaccination. The CpG molecule and SARS-CoV-2 spike protein were combined with GO solution. Stimulation of the immune system and production of antibodies occurs after the vaccination of mice, as well as a slow release of the drug. Large-scale production of graphene-based systems with antiviral effects ought to be further studied due to the low cost and simple synthesis techniques.

4. Improving the performance of carbon-based nanomaterials against COVID-19

4.1. Computational method-based optimization of carbon nanomaterials in the fight against COVID-19

Computational methods can be used in drug discovery, the progress of biosensors, and the design of receptors. These include molecular docking, QSAR, and machine learning approaches. Optimization of the 3D structure of small molecules and junction areas can be performed using docking simulations. However, this junction simulation process is somewhat tedious, especially in the case of macromolecular compounds. Notably, machine learning methods have developed the application of computational assays in the silico [144]. Machine learning can exactly investigate the association between chemical structure and interactions with proteins to produce ligand pairs. Machine learning-related systematic analysis permits the optimization of biosensors, estimation of the association of different thin-film properties, and possibly increasing the use of sensors for POC testing to highly sensitive and rapid diagnosis of viruses. CNT-based biosensors can be optimized by studying the correlation between thin-film and sensitivity by machine learning. This assay permits the systematic optimization of biosensor to act slightly than relying on human perception, which has a higher probable of accomplishing greater sensor activity. Smaller surface roughness and high CNT placement produced greater sensitivity, which can be recognized to improve the surface area for the bio-receptor binding. These nanosensors exhibited great sensitivity to identify NPs in the SARS-CoV-2 virus [145]. Molecular dynamic (MD) simulations can offer detailed molecular interactions; thus, they are broadly applied to learning the interactions among molecules and NPs. MD simulations are applied to study the interactions among materials, such as GO and M^{pro}, pointing to offer details of the interactions among them. These results help to found the interaction and inhibition of GO and other materials with M^{pro} inactivated for inhibiting viral expression successfully through destroying the active pocket of M^{pro}. This study illustrated the excellent potential of graphene-based anti-SARS-CoV-2 materials [146].

4.2. Multi-component reactions

Multi-component reactions are reactions using various starting materials where most of the atoms are joined in the product [147]. Multi-component reactions show high consideration in the synthesis of drugs or biomolecules. Besides, this assay can efficiently aid the sustainable instructions [4,148]. Among them, Ugi's four-component reaction was further employed. The Ugi 4-CR permits the production of peptides with amide functionality which establishes the backbone of one of the most chemical construction blocks used in the environment. This method is intrinsically atom economical, greatly effective, and easy to use [149]. A new covalent surface modification of MWCNTs through Ugi reaction can permit carboxamide-f-MWCNT nanovectors to start. Results revealed that this modification could cause outstanding solubility of CNTs in water and organic solvents in drug delivery vehicles. The scaffolds of carboxamide permit the loading of a greater amount of drug on the functionalized MWCNTs [150]. With a multi-component reaction, polymers comprised of CNTs and graphene derivatives can be produced to prevent bacterial binding, acting as antiviral agents. Computer simulation showed the occurrence of entropy-driven interactions among the layers of bacteria and the needles in polymers and guided to optimize these polymers to increase resistibility to bacterial binding [128].

The multi-component reaction of the electrode has a critical role in enabling electron transfer between GOx and the electrode surface. The combination of a biosensor from chitosan with polytetrafluoroethylene emulsion (PTFE)/GOx/MWCNTs/polythionine (PTH) is an efficient amperometric biosensor. The developed biosensor can be applied to the immobilization and estimation of direct

electron transfer of other enzymes and proteins [151]. Based on studies reported so far, the multi-component reaction could be applied as flexible synthetic apparatuses to fabricate an efficient biosensor for the rapid detection of SARS-CoV-2. Indeed, a multi-component reaction can integrate various bio-receptors inside a single platform; this assay could create a greatly sensitive optical sensor, as well as in DDSs.

5. Challenges, alternative approaches and future perspectives

The outbreak of COVID-19 is a worldwide subject, and in the existent condition, the progress of technologies is the extreme weapon to combat the COVID-19. Herein, the fascinating properties of carbon-based nanomaterials have been studied, including biocompatibility, antiviral/antibacterial effects, and unique chemical/electronic properties. These nanomaterials have shown excellent potentials to combat and control viral infections, providing efficient systems and equipment with antiviral and personal protective effects. Research is underway into these nanomaterials' role in controlling and treating COVID-19. The role of carbon-based nanomaterials in the progress of antiviral and photothermal masks has been deliberated. Notably, various biosensors and diagnostic kits on commercial and laboratory scales have been constructed based on carbon-based nanomaterials. One of the objects is the immune activation relationships between coronavirus and CNTs. The application of CNTs shows a progressive assay to immunotherapeutic uses based on the progress of novel nano-based products to treat different viral infections.

Despite the advantages of these nanomaterials, there is still much work to be performed to use them in nanomedicine and clinical applications:

- Further investigation of the interactions among carbon-based nanomaterials and viruses is still required.
- Additional explorations ought to be conducted regarding carbon-based nanomaterials' toxicity, metabolic paths, and biodegradation. One of the ways to decrease the toxicity of these nanomaterials is green synthesis techniques. Using greener techniques with environmentally-benign features to synthesize carbon-based nanomaterials with high biocompatibility and low toxicity using renewable and sustainable resources can prevent/reduce the toxicity and energy consumption.
- There are still limitations regarding the interactions among materials and graphene when applied in engineering PPE equipment, which can be overwhelmed through suitable modification of carbon-based nanomaterials to increase interfacial interactions. The large-scale production of carbon-based nanomaterials ought to be further explored after optimization of synthesis conditions to increase the commercialization of these materials, such as graphene, for PPE equipment.
- More elaborative studies are still required for the delivery of carbon-based nanomaterials loaded with drugs/therapeutic agents to target tissues/sites. Undoubtedly, engineering carbon-based nanomaterials with suitable functional materials can increase the plasma circulation time and reduce the concentration of required free drugs to avoid possible side effects. It is also possible to covalently modify the surface and bind the target agents to the surface of carbon-based nanomaterials through chemical bonding for specific targeting and detection with higher accuracy and sensitivity.
- One of the key limitations for developing the properties of CNTs is their dispersity and denotation in CNTs with a varied range of sizes and morphologies. However, most applications do not need discerning CNT structures; some developing applications such as biosensors require CNTs with specific structures and properties. Accordingly, comprehensive studies should be conducted MWCNTs, especially on optimization of their sizes and properties. One of the most common preparation techniques is based on the utilization of chemicals to react with a precise type of CNTs and to change their dispersion in a solution. Subsequently, common techniques such as chromatography, filtration, and centrifugation can be applied to separate these CNTs.
- Another significant limitation of carbon-based nanomaterials is their heterogeneity. Practical biosensors need reproducibility and uniformity. Suitable techniques are required for purifying these nanomaterials to yield homogeneous carbon-based biosensors. Thus, systematic studies are still demanded to find novel carbon-based nanosystems in designing next-generation electrochemical biosensors.
- Combining CNT-based sensors with other metal NPs can enhance their functionality and applicability. The development of suitable methods for tackling the challenges associated with highly selective and quick coronavirus detection is now happening in studies. The pathway "from laboratory to reality" is challenging and must be increased by enhancing the formation of high-purity and cost-effective CNTs to enable scale-up. Thus, the cost of preparation and the stability and reproducibility of CNTs must be addressed, and good control over their properties is highly recommended.

One of the significant points is the biosafety issues as a critical concern for having carbon-based nanomaterials in the market. The nanomaterials properties of CNTs are comparable to those of asbestos from potential health risks. Researchers collected data for the adverse effects of SWCNT/MWCNTs as well as carbon nanofibers from different studies [152,153]. The studies show that fibrotic lesions, lung inflammation, and genotoxicity are potential adverse health effects after the exposure to CNTs. Besides, more long-term research is required to investigate probable chronic effects and categories of CNT/CNF physical properties more precisely, which can cause possible side effects [154]. According to the reports from NIOSH, CNT and CNF should be deliberated on respiratory hazards, and the proposed exposure control limit is 1 g/m^3 elemental carbon [8].

The exposure to carbon nanomaterials through respiratory and transdermal routes is very important. Currently, occupational exposure is one of the biggest concerns. Consumer exposure in future applications should be of equal concern for future products in the early stages of research and development. Until now, internationally accepted quantitative methods for CNTs still need to be made available. The International Committee for Standardization (ISO) has published its description methods [154]. The guidelines are diversified in USA and Australia; for instance, there are no precise needs for nano-based products in the EU if their importing amounts

Table 3
Risk management guidelines of CNTs through HSE, NIOSH and Safe work in Australia.

Description	Risk management guideline		
	HSE	NIOSH	Safework Australia
Toxicity of CNTs	All CNTs can be hazardous	All CNTs/ CNFs should be preserved as possible hazards	All CNTs are hazardous
Guidelines for PPE	Development of breathing masks for various concentrations	Instructions assumed at various risk levels	Guidelines assumed at various risk levels
Risk assessment (general principles)	The worker's job and responsibilities are measured to determine potential for exposure	Current risks are measured and suitable changes should be made	Management of detailed hazard analysis and control banding
Exposure limits	Introduction limit 5 mg/m^3 by EU-OSHA	EC LOQ 1 μg/m^3	EC LOQ 1 μg/m^3 according to NIOSH
Medical assessments for workers	No permissible obligation for health surveillance but suggested keeping record by COSHH health record form Cleaning processes given	Original assessments at regular intervals	Only data collection, and duration of use

are less than 1000 kg. However, in the USA and in Australia, notifications are required for CNTs [153]. HSE and especially Safe work Australia approaches are to progress safe work environments through risk management guidelines. The effort to provide more detailed guidelines and NIOSH's strategy is to guide investors to make their guidelines. Although the NIOSH strategy is based on consistent sampling, analysis and exposure control. A summary of the risk management guides by HSE, NIOSH, and Safe Work Australia for risk management of CNTs showed in Table 3 [154].

6. Conclusions

This review delineates the recent trends in carbon-based nanomaterials for COVID-19 diagnosis, prevention and treatment. Despite the appearance of an enormous number of new techniques to address the subjects associated with the COVID-19 pandemic using different classes of nanomaterials in the literature, this topic is still in its beginning. Carbon-based nanomaterials with their robust optical/electrochemical properties, controllable sizes, biocompatibility, and cost-effectiveness have been widely applied in designing biosensors. These nanomaterials can be deployed as advanced nanosystems for targeted delivery of antiviral drug/agents, after suitable functionalization. Their properties can be improved through modification using different substrates, proposing wonderful potential for biological and biomedical applications. This review also highlighted the most critical studies and revealed the challenges required to be overwhelmed to transform scientific studies into clinical applications. Carbon-based nanomaterials can play crucial roles for the specific recognition of viruses such as SARS-CoV-2; different novel carbon-based hybrid nanosystems can be designed in combination with other nanomaterials, showing synergistic therapeutic effects along with the improved diagnostic ability. However, challenges pertaining to the biosafety and immunogenicity of these materials still need to be focused by researchers. To design nano (bio)sensors with high sensitivity and selectivity, these functionalized nanomaterials can be deployed. However, clinical translation studies and optimized conditions as well as reproducibility and cost of production are main criteria for future explorations.

Declaration of Competing Interest

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

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.onano.2023.100121.

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