Viewpoint: How the Graphene Could Help to Decrease SARS-CoV-2 Spread?

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Received: 23 November 2020, Accepted: 09 March 2021, Published online: 12 April 2021

Abstract
The COVID-19 (Coronavirus Disease 2019), caused by the SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) began in December 2019 in Wuhan, China. Until February 2021, there are 110 million of infected people, 60 million have recovered and approximately 2.5 million have passed away worldwide according to WHO. The coronavirus pandemic is evolving very rapidly and represents a risk for health care workers and society in general. Moreover, pandemic has tested the limits of health systems by raising questions about forms of prevention, management of infections with conventional therapies and the use of diagnostic tools. In this article we discussed the possible role of the nanostructured-graphene based materials as aid tools for preventing the spread and infection of SARS-CoV-2. In this regard, nanotechnology could take part in the fight against the spread of future diseases caused by deadly viruses. However, its use should be well founded in terms of biocompatibility. Therefore, we have proposed an approach based on graphene nanomaterials as possible allies for the fight against the COVID-19 spread based on the physicochemical features that present these novel nanomaterials.

Keywords
COVID-19, SARS-CoV-2, infection, graphene nanomaterials

1 Introduction
COVID-19 is the infectious disease caused by the most recently discovered member of coronavirus family, the SARS-CoV-2. The COVID-19 outbreak has been rapidly spreading around the world, resulting in an ongoing pandemic. Coronaviruses are spherical viruses in which the viral spike (S) protein forms a characteristic crown on the virus surface. The S protein promotes coronavirus entry into cells via attachment and membrane fusion. The entry of SARS-CoV-2 into human relies on its spike-protein interaction with human Angiotensin-Converting Enzyme 2 (ACE2), a human cell surface receptor that facilitates viral entry and replication [1], Fig. 1. The SARS-CoV-2 that causes the COVID-19 is transmitted primarily through droplets generated when an infected person coughs, sneezes or breathes out. These droplets are too heavy to remain suspended in the air and fall quickly into the ground or surfaces. Someone can become infected by inhaling the microparticles that contain the virus if
this person is near of a person with COVID-19 or if, after touching a contaminated surface, the person touches his eyes, nose, or mouth [2]. The COVID-19 is a highly lethal respiratory disease that has generated international anxiety due to uncertainty about its economic and social repercussions, as well as the return to daily activities [3]. The above has resulted in a huge amount of competitive and collaborative efforts in search of novel antiviral drugs, vaccines, and personal protection equipment (PPE) reaching almost desperate proportions due to catastrophic repercussions of different nature that the virus brought with it [4].

Therefore, carrying out personal care recommendations such as the use of face masks, alcohol gel to clean the hands and keeping a safe distance in crowded places is helpful in reducing the chances of contracting the infection. The rapid spread of the SARS-CoV-2 virus has challenged the industry producing biosecurity items as masks, gowns, glove, and protective screens, basically everything related to PPE. The adequate use of PPE is highly recommended to prevent new infections, especially among healthcare personal and infected patients, as well as by the rest of the population once established the recommendations by the WHO [5]. For more than a decade, nanotechnology has been linked to the world in an increasingly accelerated way and their applications have been taken to medicine. The nanotechnology potentiates the synthesis of novel materials and tools that could result in an improvement of medical devices and equipment for of health cares. Novels electroconductive nanomaterials like graphene present physicochemical properties that make it an attractive material to be used as an ally in PPE and a diagnostic tool for decreasing the virus spread [6, 7]. For example, due to its electrical properties, a protective barrier of graphene oxide in the face protection gear could interact with positively charged viruses and disable the interaction between the viruses and internal human cells. Furthermore, it is interesting to think of a synergistic effect due to its antiviral and antimicrobial activity due to electrons motion towards the core of the virus where its RNA is stored [8, 9]. Therefore, we have analyzed the potential characteristics presented by nanomaterials such as graphene and its derivatives as possible allies in the development of technology in the fight against the pandemic caused by the SARS-CoV-2.

2 Graphene derivates and virus interaction

Graphene is a two-dimensional (2D) sheet-like material with $sp^2$ hybridized carbon atoms configured in a hexagonal structure and its thickness is equivalent to an atom diameter [10, 11]. Along with its derivatives, graphene oxide (GO) and reduced graphene oxide (rGO), graphene materials have been deeply studied and applied in various fields due to the presence of aromatic rings, free $\pi-\pi$ electron and reactive functional groups [12, 13]. Graphene-based materials provide the advantages of easy preparation and reusability. Indeed, the synthesis methods of graphene and its derivatives are grouped in top-down and bottom-up approach. The top-down methods are mechanical exfoliation, arc discharge, oxidative exfoliation-reduction, liquid-phase exfoliation (LPE) and unzipping of carbon nanotubes. These methods are scalable and produce quality products. However, they show a low yield and rely heavily on the finite graphite precursor. The bottom-up methods include chemical vapor deposition (CVD), epitaxial growth, substrate-free gas-phase synthesis (SFGP), template route and total organic synthesis. However, they involve a high production cost and sophisticated operational equipment with a better product quality [12, 14]. Among all these methods, low cost and high throughput material are obtained through the direct LPE method [15]. As for its features, graphene shows attractive and favorable optical transmittance (97.7 %), high electrical and thermal conductivity, resistance ($\sim$1100 Gpa), elasticity and flexibility properties [16, 17]. Moreover, graphene is pure Carbon element, but its edge and basal plane present different electrochemical characteristics. Graphene also shows specific capacitance, high surface area (= 2630 cm$^2$/g) and rate of electron motion (200,000 cm$^2$/Vs) [14, 18]. Meanwhile, GO which is a graphene derivative, is rich in functional groups containing oxygen like carboxyl (-COOH), hydroxyl (-OH), epoxide (-O-) and carbonyl (-COO) groups. Among these oxygenated groups, the plane or basal network is formed mainly by -OH and -O- groups, while the part of the edges is formed by -COO and -COOH groups. Hence, GO is a compound structurally rich in carbon, hydrogen, and oxygen [19, 20]. By its part, the rGO is the result of the of the chemical reduction of GO. Through a reduction process, the oxygenous functional groups in the GO are almost totally eliminated to form rGO with a carbon to oxygen (C/O) ratio of 8:1–24:6:1 [21]. Graphene pure is so hydrophobic that it is difficult to disperse in the most solvents. Therefore, to enhance its solubility and electrical conductivity, the graphene can be modified by adding functional groups on the surface through chemical modification, covalent, or noncovalent functionalization [22]. Graphene can be modified either
by chemical functionalization using amines, esters, isocyanate, and polymer wraps, or by electrochemical modification using ionic liquids [15]. The modifications on graphene surface would enhance the properties of the synthesized graphene-based nanomaterials.

On one hand, among Graphene, GO and rGO, the GO has the highest negative charge and therefore, it shows a higher affinity for positively charged regions of viruses like SARS-CoV-2. In this context, Hassanzadeh et al. [23] found that the S protein of SARS-CoV-2 is slightly more positively charged than that of the first SARS-CoV virus since it contains four more positively charged residues and five less negatively charged residues which may lead to an increased affinity to bind to negatively charged regions of other molecules through electrostatic interactions. Therefore, GO could interact with viruses through electrostatic interactions, hydrogen bonding and redox reactions. Moreover, an important characteristic of graphene is the bond length between sp²-bonded carbon atoms equivalent to 0.142 nm, whereas the diameter of SARS-CoV-2 is around 65-125 nm [24], which suggests that graphene could easily retain viruses by not filtering through the honeycomb network and by electrostatic attractions, as shown in Fig. 2. In this sense, the company named Direct Plus developed a high performing graphene-based mask in order to contribute to the fight against COVID-19 making use of the bacteriostatic feature of graphene [25]. In addition, to contributing to the development of graphene-based technology for population protection, graphene could also be used in the development of new graphene-based air purification filters technology used for example in hospitals, work offices and industrial warehouse, places with exposure to virus infection. The G6 materials company have developed a unique method to incorporate graphene in the air filtration systems making them more efficient taking advantage of the extraordinary antimicrobial qualities of graphene [26]. Indeed, it has been proved that the viruses can be denatured after adsorption on graphene and heat treatment at 56 °C for 30 min [27, 28]. The potent antiviral activity of both GO and rGO also have been proven, this can be attributed to the unique single-layer structure and negative charge features. According to Ye et al. [29], the GO can inactivate the viral particles prior to their entry into cells. The electrostatic interaction offers the negatively charged sharp-edged GO more chances to interact with the positively charged virus particles, resulting in virus destruction and inactivation. Furthermore, the graphene also present antibacterial activity by electron transfer since it can act as an electron acceptor and abstract electrons from bacterial membrane, which may generate a damage in the membrane integrity [30]. By their part, the GO can destroy the bacteria by damaging the cell membrane through a chemical reaction whereas rGO can induce the mechanical stress, which pierced the cell membrane. The antibacterial activity offers the characteristic of reducing the production of bad odors due to bacterial proliferation in a mask. According to Huang et al. [31], commercial face masks shows low capacity to kill the contained bacteria and over 90 % of bacteria remain proliferative even after 8 h, whereas GO mask can decrease almost totally bacterial proliferation. Another characteristic of GO is its photocatalytic activity because the GO in combination with a narrow bandgap semiconductor can generate in the visible light region oxidizing reactive oxygen species like superoxide (O₂⁻) and hydroxyl radicals (HO) to destroy bacteria or viruses [9]. This is attributed to the graphene increases lifetime and availability of the charge carriers (h⁻/e⁻) due to the capacity of graphene to store, capture, and shuttle the electrons further favor space separation of the charge carriers [32]. This last photocatalytic property is proposed because concentrations of the SARS-CoV-2 have been identified in human fecal and wastewater samples from different countries and potential cases of transmission via wastewater have been reported [33]. However, the survival period of coronavirus in water and wastewater strongly depends on temperature, kinds of wastewater, concentration of suspended solids and organic matter, solution pH, and the dose of disinfectant used [34, 35]. Another application of graphene that is already a reality, is its incorporation into clothing. There are developments in progress to improve carbon fiber composites with graphene, which could be highly useful not only in sports equipment, but also in PPE for health care workers. For example, Tang et al. [36] designed cotton fabric with the dispersion of coated graphene oxide (GO) nanosheet on the surface of fabric via vacuum filtration deposition method. In addition, the obtained fabric was assembled with polyaniline by the in-situ chemical polymerization process. The results showed a better UV radiation protection and higher electrical conductivity compared to control cotton as well as resistance to washing without losing properties. The graphene-modified textile must be economically accessible, on a large scale and of high quality. Recently, some companies have developed the electrochemical exfoliation of graphite as a promising wet chemical method with advantages such as upscalability, solution processability and eco-friendliness. However, the quality
of graphene is still low as defects are generated during process [37, 38]. According to Xu et al. [39], the production of graphene fibers must utilize the strategy of solution assembly, which resembles the wet spinning of polymeric fibers. Moreover, there are three prerequisites that must be fulfilled to fabricate graphene fibers with a high quality:

- scalable synthesis of solution-processable graphene,
- continuous regular alignment of graphene and
- re-engineering of bonds among graphene building blocks.

Graphene-based clothing offers very attractive characteristics (Fig. 2) such as light weight, flexibility, elasticity, fire retardancy, hydrophobicity, UV protection, antibacterial, antiviral and antifungal activity, thermal regulation, and durability of the clothing [40]. Therefore, graphene modification of textiles shows a potential in this and future pandemics.

3 Graphene biosensors for virus detection

Most of the diagnostic test available for SARS-CoV-2 are based on Polymerase Chain Reaction (PCR) procedure. This technique offers sensitivity and specificity for the identification of a viral infection. However, it is a slow test, it needs trained personal and expensive instruments. In search of a faster and economically accessible diagnosis test due to high demand, affinity-based biosensors can provide alternative solutions to diagnostic of possible SARS-Cov-2 cases [41]. Biosensor refers to an analytical device that produces a measurable signal proportional to the concentration of an analyte or target. Graphene has great electrochemical, mechanical, and thermal properties which influence their application in biosensors [42]. Biomolecules as antibodies, enzymes and DNA can be easily incorporated on graphene surface for the detection of a target molecule. The biosensors consist of a receptor and a transducer, Fig. 3. The receptor is the part that interact specifically with the target molecule [43]. The target molecule can be organic, inorganic or cells, whereas the transducer is the part of the sensor, which converts chemical information into a measurable electrical response [44]. Hence, the presence or concentration of a target molecule can be identified due to graphene can facilitate the electron transfer between the bioreceptor and transducer, which can generate high signal sensitivity for electrochemical sensors. The selectivity and sensitivity of graphene can be improved by its surface modification with suitable functional groups. This graphene surface modification enables tuning of the optical and electrical properties, which is fundamental for the virus detection in graphene-based systems [45]. Different approaches for sensing biomolecules as nucleic acids, peptides, enzymes, and antigens have been designed based on physicochemical methods providing an electrical, electrochemical, and optical signal. The most common optical sensing methods for virus detection are photoluminescence-based biosensors, colorimetric biosensors, graphene-based surface plasmon resonance biosensors and surface-enhanced Raman spectroscopy, whereas the most common electrochemical sensing methods are the electrochemical sensing based on antigen–antibody biospecific recognition interaction and the electrochemical sensing based on DNA hybridization [46]. In addition, these methods based on optical and electrical signals are very attractive due to the accessible instrumentation. Therefore, due to the electrical and optical properties of graphene-based nanomaterials, this kind of nanomaterials are highly suitable for virus detection.

For example, Omar et al. [47] developed an optical sensor for the Dengue virus (DENV) E-protein based on cadmium sulfide quantum dots composited with amine functionalized graphene oxide (CdS-NH2GO) thin film. They found that the sensor exhibited an excellent detection limit (0.001 nM/1 pM) with sensitivity of 5.49° nM−1 for the detection of DENV E-protein, whereas the binding affinity with Au/CdS- NH2GO/EDC-NHS/IgM and E-protein was 486.54 nM−1 for detecting DENV E-proteins. In another...
work, Afsahi et al. [48] developed a cost-effective and portable graphene-enabled biosensor to detect Zika virus with a highly specific immobilized monoclonal antibody. This biosensor is capable of detecting doses of antigen as low as 0.45 nM. Authors argued that the speed, sensitivity, and selectivity of this first-of-its-kind graphene-enabled Zika biosensor make it an ideal candidate for development as a medical diagnostic test. In another study, Oliveira et al. [49] reported the development of an electrochemical genosensor for the diagnosis of Hepatitis C virus (HCV) in real samples based on a gold electrode modified with GO and ethylenediamine. The modification was useful to probe DNA immobilization following interaction with the target DNA HCV through hybridization. Authors argued that the developed electrochemical genosensor was specific and selective in identifying HCV-gRNA, isolated in human serum from different infected patients, translating this biorecognition event into a measurable signal in only 20 min of test, with a detection limit of 1.483 (v/v) or 1.36 nmol·L⁻¹ of RNA.

In other cases, Islam et al. [50] designed a smart nanosensor for the detection of human immunodeficiency virus (HIV) using graphene-based field-effect transistors (FETs). In this study, the authors functionalized graphene with amino groups for covalent conjugation of antibodies (anti-p2) on the graphene surface via carbodiimide activation. The electrochemical performance of the sensor was evaluated with respect to changes in the resistance of the electrode surface due to the interaction of the antigen with its specific antibody. Authors mentioned that sensor was highly sensitive and concluded that graphene can be an extremely sensitive platform for the detection of HIV and related cardiovascular diseases and arthritis. In another study of virus detection, Anik et al. [51] developed an effective electrochemical influenza A biosensor based on graphene-gold (Au) hybrid nanocomposite modified Au-screen printed electrode. The working principle of the sensor involved observing neuraminidase activity. After the optimization of experimental parameters, the analytical characteristics of the influenza A biosensor were investigated. However, despite the sophisticated construction of the biosensor, a very low limit of detection value of 10⁻⁸ U mL⁻¹ was achieved. As previous studies have been shown, graphene-based biosensors are quite useful for virus detection. Therefore, due to global health crisis that SARS-CoV-2 has produced, a rapid and sensitive sensor for the SARS-CoV-2 detection has been development. Recently, Seo et al. [52] developed an high sensitivity field-effect transistor (FET)-based biosensing device for detecting SARS-CoV-2 in clinical samples, Fig. 4. The sensor was produced by coating graphene sheets of the FET with a specific antibody against SARS-CoV-2 spike protein. According them, the FET device could detect the SARS-CoV-2 spike protein at concentrations of 1 fg/mL in phosphate-buffered saline and 100 fg/mL clinical transport medium. In addition, the experimental results showed that their biosensor could be a candidate for fast screening SARS-CoV-2 patients in early stages of the disease, with advantages as of low-cost and ease of use.

On the other hand, graphene must compile excellent optical, electrical, thermal, electrochemical, and textural features for biosensor applications. The micromechanical exfoliation of highly ordered pyrolytic graphite, epitaxial growth, and CVD can produce graphene with a relatively perfect structure with excellent properties. Graphene fabricated by such methods is commercially available but in small quantities, and their prices are generally larger in line with their superior quality [53]. The use of graphene-based nanotechnology for biosensors can reduce the cost, time, and facilitate the production of commercial devices. The graphene-based biomaterials are ideal platforms for electrochemical biosensors due to their good electrical and thermal conductivity, flexibility, high surface area, light weight, and biocompatibility. Moreover, the graphene with a low environmental impact, it is a promising material for the construction of devices in various transduction modes, from electrical and electrochemical transduction to optical transduction [54].

4 Graphene toxicity

Despite several achievements, there are still some difficulties and challenges associated with graphene-based materials. The toxicity of graphene is a matter of debate. The majority of current literature agree that unmodified graphene, GO and rGO are cytotoxic and/or genotoxic [55].

Fig. 4 Schematic representation of the operating procedure of the SARS-CoV-2 -FET biosensor (adapted from [52]).
However, the dose is one of the most critical factors and some researchers propose that low doses of graphene may be safe (lower than 0.25 mg) [32]. Even, at low doses, it could function as an enhancer for cell proliferation [56]. However, the physicochemical properties of graphene as the particle size, lateral size, functionalization, charge, impurities, particulate state, synthesis route, reactive oxygen species production, surface functional groups, and oxygen content/surface charges may significantly affect their toxicity in biological systems [57]. The exposure routes of humans to nanomaterials are via inhalation, ingestion, eye, and skin contact exposure, parenteral or intravenous route, especially by intentional administration. Furthermore, the degree of toxicity depends strongly on the route of exposure. In this context, the skin constitutes one of the major exposure sites to graphene materials, not least if it is used to develop EPP. Regarding cutaneous toxicity, skin disorders, e.g., irritation, sensitization and contact dermatitis may be considered after a cutaneous exposure given the graphene chemical nature and the capability of graphene-based nanomaterials to interact with proteins [38, 58]. Nevertheless, except for one in vivo dermal study showing local inflammatory response after 2 days of graphene-based nanomaterials which is resolved in no more than 7 days [59], majority data comes from in vitro studies in cell lines and suggest a potential cytotoxic effect associated with production of reactive oxygen species [60]. However, existing information of dermal in vivo and in vitro toxicity is still very limited, and more studies are needed to draw conclusions of the risk related to dermal exposure. According to Volkov et al. [61], the accumulated experimental evidence shows that there is still a considerable amount of uncertainty and sometimes controversy over the current findings related to the biocompatibility, toxicity and potential applications of graphene-based nanomaterials. This is attributed to the differences in the experimental setups and approaches from each research team and to wide diversity of graphene forms and synthesis routes. Long-term exposure effects must be deeply investigated to obtain more complete toxicological information.

5 Conclusions and prospects

The SARS-CoV-2 has taken the lives of many people and will inevitably continue to affect other millions of persons. The use of adequate PPE and clear procedures on its application will be necessary to decrease the spread of the virus. The WHO continues to recommend the daily use of protective accessories such as face masks and other protective barrier equipment. We have proposed a hypothetical possibility of the use of graphene as an ally for decreasing COVID-19 cases. Graphene could play a role as a support agent when used as a protective textile coating against viruses. In fact, its application in clothing market is already a reality. We believe that the need for the development of tools to prevent the spread of SARS-CoV-2 has motivated scientists and entrepreneurs to design and market clothing, air filters, biosensor technology and other commonly accessible tools in response to the wave of health and economic effects that the virus brought with it. We have proposed the use of graphene as an ally against the SARS-CoV-2 spread due to the wide range of possibilities of use based on its physico-chemical features. Fig. 5 shows a schematic of the potential use of graphene and its derivatives for combating COVID-19. Furthermore, the coronavirus outbreak could accelerate the development of new nanomaterials with applications in future pandemics [62], for example, the use of sprays for cleaning surfaces with a longer duration, the manufacture of antiviral casual clothing and retrovirals with programmed dose release. However, its use must be accompanied by intensive toxicity studies that support its safe use.

Acknowledgement

This work was supported by the National Council for Science and Technology (CONACYT) with the scholarship No. 633566. The authors declare that they have no known competing financial interests that could have appeared to influence the work reported in this paper. Dedicated to the memory of V. F. Marañón-Ruíz.
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