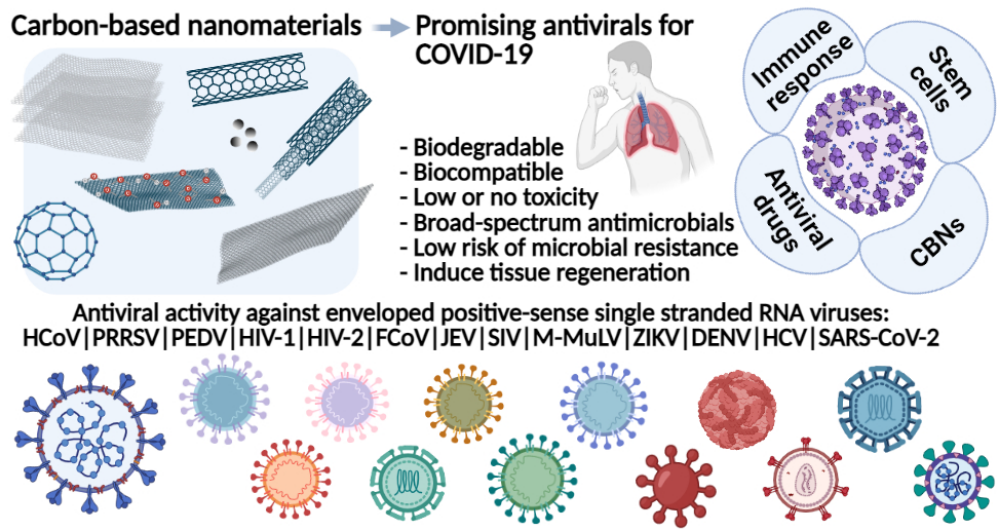


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Carbon-Based Nanomaterials: Promising Antiviral Agents to Combat COVID-19 in the Microbial Resistant Era

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Carbon-Based Nanomaterials: Promising Antiviral Agents to Combat COVID-19 in the Microbial Resistant Era

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Abstract

Therapeutic options for the highly pathogenic human Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2) causing the current pandemic Coronavirus disease (COVID-19) are urgently needed. COVID-19 is associated with viral pneumonia and acute respiratory distress syndrome causing significant morbidity and mortality. The proposed treatments for COVID-19 have shown little or no effect in the clinic so far. Additionally, bacterial and fungal pathogens contribute to the SARS-CoV-2 mediated pneumonia disease complex. The antibiotic resistance in pneumonia treatment is increasing at an alarming rate. Therefore, carbon-based nanomaterials (CBNs), such as fullerene, carbon dots, graphene, and their derivatives constitute a promising alternative due to their wide-spectrum antimicrobial activity, biocompatibility, biodegradability, and capacity to induce tissue regeneration. Furthermore, the antimicrobial mode of action is mainly physical (*e.g.*, membrane distortion), characterized by a low risk of antimicrobial resistance. In this review, we evaluated the literature on the antiviral activity and broad-spectrum antimicrobial properties of CBNs. CBNs had antiviral activity against 13 enveloped positive-sense single-stranded RNA viruses, including SARS-CoV-2. CBNs with low or no toxicity to humans are promising therapeutics against COVID-19 pneumonia complex with other viruses, bacteria, and fungi, including those that are multidrug-resistant.

Keywords: COVID-19, SARS-CoV-2, carbon-based nanomaterials, fullerene, carbon dots, graphene, antiviral properties, pneumonia, tissue regeneration

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3 History has repeatedly manifested that pathogens cause disastrous effects on human
4 beings. Thus, the recent outbreak of the recent Severe Acute Respiratory Syndrome-
5 Coronavirus 2 (SARS-CoV-2), which causes Coronavirus disease 2019 (COVID-19),
6 spread to more than 200 countries, is a clear example. The current confirmed global
7 COVID-19 cases and deaths have reached more than 90 million and more than 2 million,
8 respectively.¹ Nevertheless, experts have suggested that many more undetected or
9 asymptomatic cases exist,² especially in underdeveloped countries. COVID-19 continues
10 to spread globally, threatening to collapse the health system of many developed countries
11 such as United Kingdom and France that have been forced to go to a third lockdown.
12 SARS-CoV-2 is an enveloped positive-sense, single-stranded RNA virus.³⁻⁵ Its origin to
13 this date remain enigmatic, however multiple hypotheses have been postulated so far.⁶
14 However, the host tropism/adaptation pattern raised questions concerning the origin of
15 SARS-CoV-2.⁷ SARS-CoV-2 is the seventh coronavirus known to infect humans easily^{8,9}
16 and only the third one causing severe pneumonia.¹⁰ Viral pneumonias may be
17 complicated by secondary microbial infections.¹¹ Thus, co-infection can be caused by
18 viruses in the setting of community-acquired bacterial pneumonia.¹²⁻¹⁴ Co-infection of
19 COVID-19 patients is seen with the most common type of bacterial pneumonia caused
20 by *Streptococcus pneumoniae*.¹⁵ There is a great concern about the rapid spread of
21 pathogens, such as SARS-CoV-2 that can coexist with a broad range of other types of
22 clinically relevant microorganisms, including those which are multidrug-resistant.
23 Therefore, the co-infection of SARS-CoV-2 with other viruses, bacteria, or fungi
24 constitutes a real life-threatening to humans during the approaching cold season. In this
25 regard, several medications have been proposed which include remdesivir,
26 hydroxychloroquine, lopinavir/ritonavir, interferon β -1a, tocilizumab, favipiravir,
27 plitidepsin, convalescent plasma infusions and monoclonal antibodies, among many
28 others.¹⁶ However, presently, there is no effective treatment for COVID-19.^{17,18}
29 Furthermore, antibiotic resistance in bacterial pneumonia treatment is a wide-spread
30 problem.¹⁹⁻²¹ Therefore, in the quest to finding therapeutics for COVID-19, carbon-based
31 nanomaterials (CBNs) are emerging as promising options that have shown potent
32 antiviral activity against a broad range of enveloped positive-sense single-stranded RNA
33 viruses,²² including SARS-CoV-2, and showed low to no toxicity in humans.²³⁻²⁸ Besides,
34 they exert an effective biocidal action against a broad spectrum of bacteria, viruses and
35 fungi, including multidrug-resistant strains.²⁹⁻³¹ These CBNs are mainly composed of
36 carbon, an essential element in the human body,³² are thus biodegradable, biocompatible
37 and can induce tissue regeneration.³³⁻³⁷ Moreover, the development of CBNs as antiviral
38 agents is possible because they possess a high surface area that allows its
39 functionalization or interaction with biocompatible polymers which further enhance their
40 biocompatibility and therapeutic efficacy. The epithelial response to viral challenge is
41 well-documented to involve autophagic and apoptotic cell death.³⁸ Indeed, the primary
42 receptor for SARS-CoV-2, the carboxypeptidase ACE-2, is a protective "survival factor"
43 for human lung alveolar epithelial cells (AECs),³⁹ but is significantly reduced by SARS-
44 CoV2 infection.⁴⁰ The cells which express the most ACE-2 in the human lung alveoli, the
45 type II AECs, normally serve as stem cells for regeneration of lost alveolar epithelia,⁴¹
46 but are killed by viral challenge. For these reasons, any potential therapeutic that exerts
47 both antiviral activity and the capacity to stimulate tissue regeneration would be expected
48 to promote lung tissue repair in the face of ongoing viral-induced cell death. Research in
49 this area is still in its early stage, though it is predicted to grow exponentially due to the
50 grave consequences caused by the current pandemic. The increasing number of
51 multidrug-resistant pathogens announced by the World Health Organization constitutes
52 another real threat to humanity in this microbial resistance era.⁴² Therefore, there is an
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3 urgent need to find alternative antimicrobial strategies to curb the drug-resistance
4 menace, thus providing a long-lasting treatment for the COVID-19 disease. This review
5 addresses the application of these broad-spectrum CBNs as antimicrobial agents by
6 analyzing a large number of antiviral studies performed so far with CBNs against
7 enveloped positive-sense single-stranded RNA viruses, looking at their toxicity and
8 biodegradability, and deciphering how they could defeat microbial resistance. This vision
9 could surpass substantially any technological paradigms that currently exist or are under
10 development a part of advanced therapeutics to treat COVID-19.
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13 **Next Generation of Antimicrobials: Carbon-Based Nanomaterials**

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16 Antiviral activity of viral infection compounds can be classified into two different
17 subgroups: (1) virus-inhibiting compounds (usually cellular); or (2) compound that
18 augments host defense improving or altering virus infections (immunomodulating
19 agents).⁴³ Antiviral mechanisms usually require an inhibitory effect of a particular viral
20 cell cycle essential in viral replication. As viral replication mainly depends on the host
21 cell's metabolism as viruses are obligate intercellular parasites, valuable antivirals can
22 disrupt viral-specific functions or at least obstruct virus-directed functions as opposed to
23 the host cell. Therefore, the spectrum of antivirals generally is restricted. Many existing
24 antiviral agents block host cell surface attachment followed by conformational changes
25 of the viral capsid, leading to the uncoating of the viral genome, preventing the virus from
26 penetrating the target cell. Others, such as nucleoside or nucleotide analogs, are antiviral
27 drugs that provide an impairment of nucleic virus synthesis as their mode of action. An
28 essential factor for antiviral activity is the inhibition of virus attachment to a cellular
29 receipt or viral entry, inhibiting the viral from entering the cells. Many viruses involve
30 proteolytic cleavage of polypeptides precursors utilizing protease inhibitors as antivirals
31 to active, vital viral proteins. Some of the antivirals inhibit the integration of the viral
32 genome with the host cells' genome. Other antivirals inhibit the uncoating (viral
33 disassembly) and therefore distributing the viral life cycle. Finally, the inhibition of the
34 virus release from the host cells through the prevention of viral clumping and thus
35 inhibition cell-to-cell movement of viruses through enzymatic inhibition.⁴⁴⁻⁴⁶

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37 To control the ever-increasing range of infections caused by multidrug-resistant
38 microorganisms and viruses,⁴² the use of antibiotics or alternative antimicrobial agents
39 such as the ionic and/or oxidized form of metals,⁴⁷ quaternary ammonium compounds,⁴⁸
40 peptoids,⁴⁹ α -peptides⁵⁰ and β -peptides⁵¹ present diverse problems including drug
41 resistance after long-term utilization. In this regard, alternative materials such as CBNs
42 with intrinsic broad-spectrum antimicrobial activity⁵²⁻⁶³ represent a promising option that
43 would probably overcome the microbial resistance problem due to their differential
44 antimicrobial mechanisms. Thus, the antimicrobial action of CBNs, such as graphene (G)
45 is often attributed to a combination of several physical and chemical mechanisms: directly
46 on the microbial particle such as (peptidoglycan membrane structure disruption,
47 entrapment of microorganisms, transfer of electrons) and and/or indirect through
48 induction of oxidative stress by reactive oxygen species (ROS).^{64,65} Other nanomaterials
49 such as those based on silver, copper, titanium or zinc nanoparticles, for example, have
50 shown strong broad-spectrum antimicrobial properties.^{47,66-69} However, the existence of
51 microbial resistance to these nanomaterials,⁷⁰⁻⁷⁶ and their high toxicity to mammalian
52 cells⁷⁷⁻⁸¹ render these materials less promising for long-term therapeutics. Therefore,
53 CBNs are increasingly proposed as the next generation of antimicrobials against
54 multidrug-resistant infections. They possess unique properties that include very high
55 surface area, excellent electrical and thermal conductivity, biocompatibility, and the
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possibility to be combined with engineered polymers to develop advanced antimicrobial biomaterial composites.^{29,82-86} Furthermore, a recent study about the paramount concern of this proposal regarding to the interaction of CBNs with the respiratory system showed that a single exposure of several CBNs (at ~ 0.3 and $1 \mu\text{g}/\text{cm}^2$) did not manifest any adverse effects under acute exposure scenarios after 24 h.⁸⁷ Regarding the biodegradability of CBNs, it has been demonstrated that the human myeloperoxidase, a peroxide enzyme released by neutrophils, degraded graphene and its derivatives^{88,89} leading to biodegradation of graphene-based nanomaterials (GBNs) in the blood after 14 days.⁹⁰ Some signals of *in vivo* degradation of graphene were reported in the lungs, liver, kidneys and spleen upon 90 days.⁹¹ Oxidized forms of GBNs have shown higher susceptibility to degradation than the reduced forms.⁹² The degradation products of graphene oxide (GO) with different dimensions exhibited no genotoxicity to human lung cells.⁹³ *In vivo* studies have shown that a concentration of $1.0 \text{ mg}/\text{kg}$ of small GO particles (148-160 nm) tends to accumulate mainly in the liver with a lower amount in the spleen and lungs, and remain longer in circulation than large ones (556-780 nm),⁹⁴ which were mostly present in lungs. However, when the concentration of injected GO, increased 10-folds, the smaller GO particles accumulated in the lungs instead of the liver thereby potentially increasing its efficacy for treating pulmonary infections. GO and reduced GO (rGO) of different lateral dimensions (10-800 nm) in a concentration of $1 \text{ mg}/\text{kg}$ exhibited long blood circulation times of 14 days after intravenous administration in mice and low uptake by the endothelial reticulum. No pathological variations were detected in the analyzed organs.⁸⁶ Biodegradation and cytotoxicity towards different cell lines depended on concentration, exposure time, oxidation degree, lateral size, and cell type⁹⁵⁻⁹⁸ and could be modified by functionalization.^{95,99-102} Smaller and more oxidized GBNs seem to be more cytocompatible than non-oxidized and larger particles.¹⁰⁰ Proteins, such as bovine serum albumin, adsorbed on the GBNs' surfaces, seem to have a protective effect on the hemolytic potential.¹⁰³⁻¹⁰⁶ The biocompatibility of CBNs depends on their concentration, oxidation degree, lateral size and dispersibility.¹⁰⁷⁻¹¹⁵ The inflammation, and other effects on cells and blood components are minimal when a lower concentration of CBNs is applied. Oxidized and smaller GBNs are more biocompatible and accessible to biodegradation in the body. CBNs have shown the potential to support the growth, proliferation, and differentiation of stem cells into different tissue lineages.^{35,116} These features potentiate the use of CBNs in combination with stem cell therapies for tissue regeneration as well as for COVID-19 patients. SARS-CoV-2 infection is accompanied with many physiopathological changes and could reach all human organs harnessing several pathways,¹¹⁷ during this it reaches and damages the vascular endothelial cells. CBNs can induce the production of angiogenic factors which initiate a series of signaling pathways to induce angiogenesis through promoting the proliferation and differentiation of endothelial cells or mesenchymal stem cells (MSCs).¹¹⁸⁻¹²⁰ In addition to the MSCs are not infected with SARS-CoV-2, of note that the stem cells (specially the mesenchymal stem) represent one of promising strategy for COVID-19 therapy, specifically those in moderate and/or severe infection.¹²¹⁻¹²⁴ Besides, MSCs downregulate Th1 and Th17 inflammation immunity and upregulate the anti-inflammation immunity of Th2 and Treg cells, it enhances the recruitment and proliferation of many productive cells and supportive materials (collage and extracellular matrix). Because of its potential, up to 21.02.2021, nine (out of ninety-one) clinical trial has been completed.¹²⁵ MSC are capable to self-replication and differentiation into specialized functions to replacing the disrupted and/or dysfunctions cells/tissues.¹²⁶ SARS-CoV-2 induces its pathological changes *via* exacerbate cytokines production which leading to many complications may reach to severe in some cases. Stem cells have specific cytokines¹²⁷ that tightly derive

immunomodulation (Figure 1) which may not only be helpful in control the SARS-CoV-2 infection severity,^{126,128–130} but extend to beyond patient recovery specifically from severe infection.¹³¹

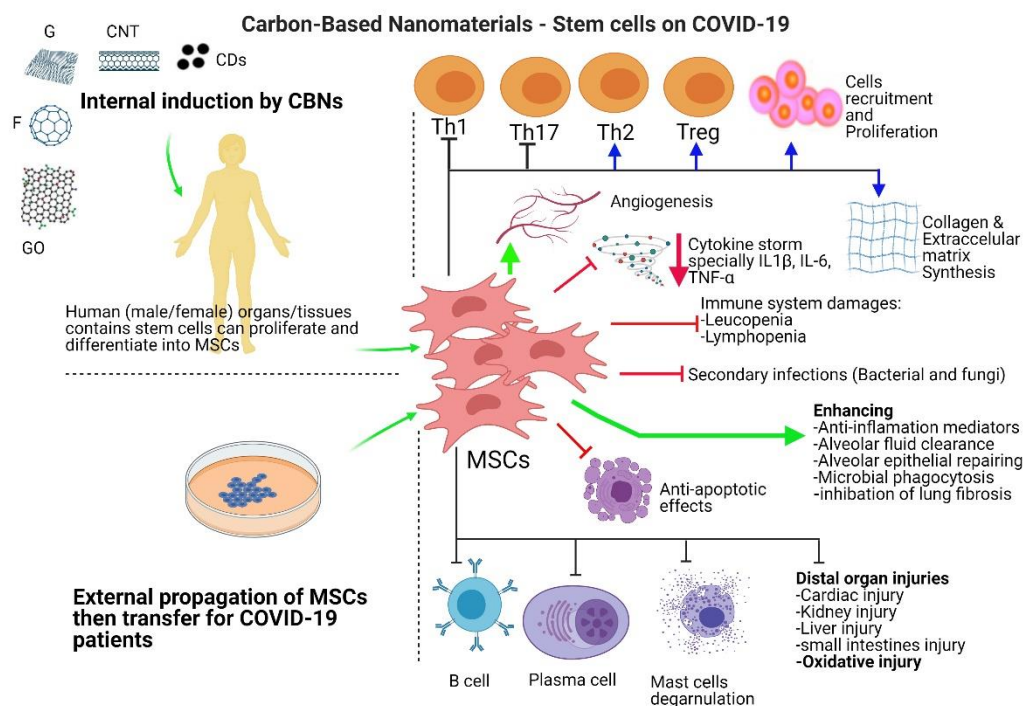


Figure 1. General panorama for external propagated and differentiated mesenchymal stem cells (MSCs) or internal induced of many tissues contains MSCs by CBNs (G: graphene, GO: graphene oxide, F: fullerene, CDs: carbon dots or CNT: carbon nanotubes). MSCs have various roles in COVID-19 and/or recovered patients through secretion and modulation of physiological and immunological networks. SARS-CoV-2 infection causes many pathophysiological changes such as tissue inflammation, immune system damages (leukopenia, lymphopenia), respiratory microstructures and distal organs injury and secondary infections, and microvascular system. CBNs in combination with MSCs have the potential to target these pathophysiological events, acting as an alternative strategy for treating COVID-19 patients.

Antiviral Properties of Carbon-Based Materials

This section analyzes the antiviral properties of CBNs with different carbon-based structures (Figure 2), such as fullerene, carbon dots, graphene, and derivatives against 13 enveloped positive-sense single-stranded RNA viruses, such as SARS-CoV-2.

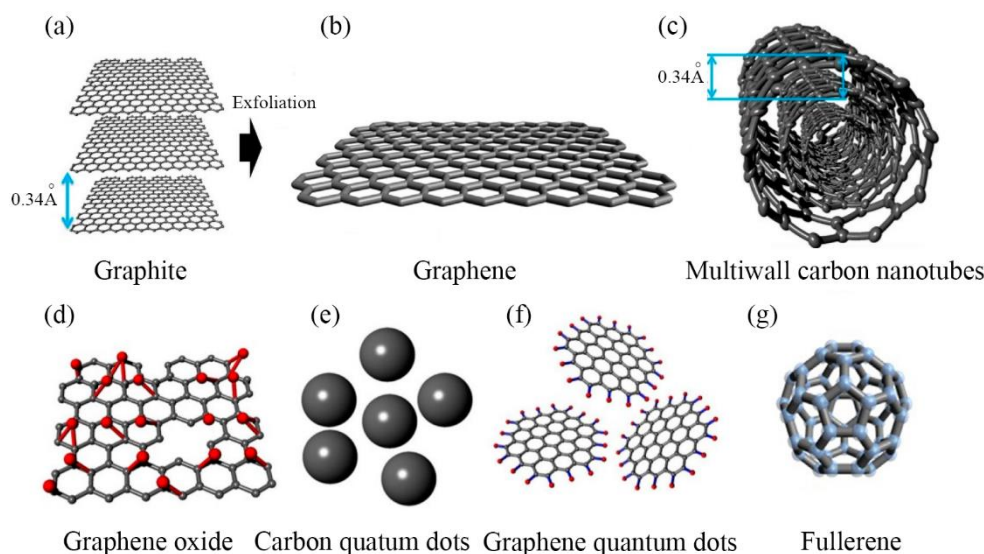


Figure 2. Main carbon-based structures studied against enveloped positive-sense single-stranded RNA viruses: (a) Graphite. Reprinted in part with permission under a Creative Commons CC BY 4.0 License from ref 133. Copyright 2019 MDPI; (b) Graphene. Reprinted in part with permission from ref 132. Copyright 2019 Elsevier; (c) Multiwall carbon nanotubes. Reprinted in part with permission under a Creative Commons CC BY 4.0 License from ref 133. Copyright 2019 MDPI; (d) Graphene oxide. Reprinted in part with permission under a Creative Commons CC BY 4.0 License from ref 133. Copyright 2019 MDPI; (e) Carbon quantum dots. Reprinted in part with permission under a Creative Commons CC BY 4.0 License from ref 133. Copyright 2019 MDPI; (f) Graphene quantum dots. Reprinted in part with permission under a Creative Commons CC BY 4.0 License from ref 133. Copyright 2019 MDPI; (g) Fullerene. Reprinted in part with permission from ref 132. Copyright 2019 Elsevier.

Fullerene and Derivatives

Fullerene is a zero-dimensional allotrope of CBNs with antiradical and antioxidant properties.^{134,135} Due to the high hydrophobicity character of pristine fullerene, antiviral fullerene derivatives can be synthesized to produce hydrophilic drugs that can be easily dispersed in aqueous media.³⁰ Studies on fullerenes as antiviral agents started in 1993 on human immunodeficiency virus type 1 (HIV-1) infections.¹³⁶ In that study, compound 1 showed effective *in vitro* antiviral activity. Another study showed that a bis(monosuccinimide) derivative of p,p'-bis(2-aminoethyl)diphenyl-C₆₀ was actively inhibiting the HIV-1 and also the type 2 (HIV-2) in acutely or chronically infected human lymphocytes and against 3'-azido-3'-deoxythymidine-resistant HIV-1. Another subsequent study showed a water-soluble fullerene-peptide conjugate capable of interacting, albeit weakly, with the HIV-1 protease.¹³⁷ In 1996, nine functional derivatives of C₆₀-fullerene compounds displayed antiviral capacity at low micromolar concentrations.¹³⁸ Furthermore, three of these compounds exhibited antiviral activity at lower concentrations than any fullerene derivative reported to that date. In 1997, nonderivatized fullerene (buckminsterfullerene) showed *in vitro* antiviral activity against another 2 enveloped positive-sense single-stranded RNA viruses similar to SARS-CoV-2: the Moloney murine leukemia virus (M-MuLV) and the simian immunodeficiency virus (SIV).¹³⁹ However, a study performed in 2003 tested a series of fullerene derivatives

(13 in total, compounds 1-13) against HIV-1 and HIV-2. The results of that study showed that some of these CBNs (6 (*trans*-2), 7 (*trans*-3) 8 (*trans*-4), 9 (*equatorial*), 12 (*trans*-2)) exhibited potent antiviral activity against HIV-1 but not HIV-2 in the low micromolar concentration range.¹⁴⁰ Nonetheless, cationic fullerene derivatives showed broader anti-HIV properties.¹⁴¹ In 2007, chlorofullerene was developed as a precursor for the straightforward synthesis of antiviral fullerene derivatives against HIV with high solubility in water.¹⁴² A later study in 2011 showed that derivatives of C₇₀-fullerene (*i.e.*, the fullerene molecule consisting of 70 carbon atoms) exhibited high water-solubility and virucidal activity against HIV and influenza virus.²⁶ A series of fullerene derivatives (Figure 3) showed potent viral inhibition of hepatitis C virus (HCV).¹⁴³

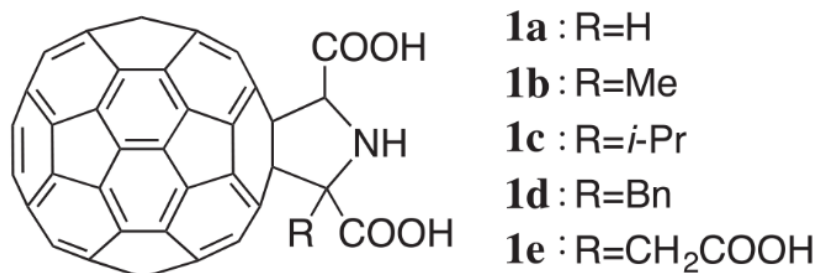


Figure 3. Chemical structure of fullerene derivatives 1a-1e. Reprinted with permission from ref 143. Copyright 2016 Elsevier.

Recently, tridecafullerenes appended with up to 360 1,2- mannobiose showed outstanding antiviral activity against Zika virus (ZIKV) and Dengue virus (DENV).²⁴ Examples of antiviral studies performed with fullerenes and their derivatives are summarized in Table 1.

Table 1. Studies analyzing the antiviral properties of carbon-based nanomaterials (fullerene, carbon dots, graphene and derivatives) against 13 enveloped positive-sense single-stranded RNA viruses. Source and manufacture of the CBNs, 50% cytotoxic concentration (CC50), half maximal effective antiviral concentration (EC50), tested viruses, tested cell line/inhibition, year and references are indicated for each study.

| Fullerene and Derivatives | Source and Manufacture | Toxicity (CC50) | Antiviral (EC50) | Tested viruses | Tested cell line/inhibition | Year | Ref. |
|---|--|--|--|--|--|------|------|
| Fullerene derivatives (Compound 1) | Synthesis of bis(phenethylamino-succinate)-C ₆₀ | None (compound 1) | 7 μM | HIV-1 | PBMC/HIV-1 protease | 1993 | 136 |
| Memethanofullerene (2c) | Synthesis of diamido diacid diphenyl fulleroid derivative | Not tested | Effective at 1 mg/ml | HIV-1 and HIV-2 | HIV- 1 and HIV-2 protease and reverse transcriptase | 1993 | 144 |
| Derivatized C ₆₀ Fullerene | Synthesis of bis(monosuccinimide) derivative of p,p'-bis(2-aminoethyl)diphenyl-C ₆₀ (compound 1) | >100 μM (compound 1) >640 μM (phosphonoformate) >100 μM (3'-Azido-3'-deoxythymidine) | HIV-1 10.8 μM, HIV-2 5.5 μM HIV-1 not tested, HIV-2 0.44 μM HIV-1 >100 μM, HIV-2 0.003 μM | HIV-1 and HIV-2 | PBM, H9, Vero, and CEM /HIV-1 protease | 1993 | 145 |
| Bioactive fullerene peptide | Synthesis of synthon 1,2-dihydro-1,2-methanofullerene [60]-61-carboxylic acid covalently linked to the α-amino group of the hydrophilic 4-8 sequence of peptide T | Not tested | 6 nM | HIV-1 | HIV-1 protease | 1994 | 137 |
| Functional derivatives of C ₆₀ -fullerene | Synthesis of fullerene derivatives (9 active compounds) | >100 μM (compound 1) >100 μM (compound 2) >100 μM (compound 3) | 7.3 μM 2.5 μM 0.9 μM | HIV-1 | PBMC and Vero | 1996 | 138 |
| Nonderivatized fullerene (buckminsterfullerene) | C ₆₀ of Gold Grade purity (Hoechst AG, Frankfurt, Germany) | Not tested | 3 μM | SIV and M-MuLV | MT-2 (for SIV) and M-MuLV reverse transcriptase inhibition | 1997 | 139 |
| Bis-functionalized fullerene derivatives bearing two or more solubilizing chains | Synthesis of fullerene derivatives (13 compounds tested) | 4.79 μM (trans-2) 3.02 μM (trans-3) 13.2 μM (trans-4) 6.59 μM (equatorial) | 0.40 μM 0.96 μM 2.60 μM 1.60 μM | HIV-1 and HIV-2 (effective against HIV-1, but not HIV-2) | CEM | 2003 | 140 |
| Cationic fullerene derivatives | Synthesis of a series of regioisomeric bis-fulleropyrrolidines bearing two ammonium groups (compounds 3-7) | 2.93 μM (compound 3) 9.04 μM (compound 4) 12.5 μM (compound 5) | HIV-1 0.21 μM, HIV-2 0.2 μM HIV-1 0.35 μM, HIV-2 0.70 μM HIV-1 1.08 μM, HIV-2 2.50 μM | HIV-1 and HIV-2 | CEM | 2005 | 141 |
| Polycarboxylic fullerene derivatives using chlorofullerene as a precursor | Friedel-Crafts arylation of C ₆₀ C ₆₆ with methyl esters of phenylacetic and benzylmalonic acids | >63 μM (compound 4a) 2.9 μM (compound 7) 9.0 μM (compound 8) | HIV-1 1.2 μM, HIV-2 4.4 μM HIV-1 0.21 μM, HIV-2 0.2 μM HIV-1 0.35 μM, HIV-2 0.7 μM | HIV-1 and HIV-2 | CEM | 2007 | 142 |
| Polycarboxylic derivatives of C ₇₀ -fullerene | Synthesis of C ₇₀ [p-C ₆ H ₄ (CH ₂) _n COOH] ₈ (n = 2, 3) starting from chlorinated [70]fullerene precursors C ₇₀ Cl ₈ and C ₇₀ Cl ₁₀ | >43 μM (compound 2aK) >86 μM (compound 2bK) | HIV-1 1.8 μM, HIV-2 23 μM HIV-1 3.3 μM, HIV-2 17 μM | HIV-1 and HIV-2 | CEM and MDCK | 2011 | 26 |
| Fullerene derivatives (1a, 1b, 1c, 1d, 1e) | Synthesis of proline-type fullerene derivatives | Not tested (compound cis-1a) Not tested (compound trans-1a) | NS5B 0.29 μM, NS3/4A 0.15 μM NS5B 0.23 μM, NS3/4A 0.85 μM | HCV | NS5B polymerase and HCV NS3/4A protease | 2016 | 143 |
| Tridecafullerenes appended with up to 360 1,2-mannobiosides | Synthesis of multivalent disaccharide/[60]fullerene nanoballs | >10 μM (compound 32) | ZIKV 67 pM, DENV 35 pM | ZIKV and DENV | Jurkat | 2019 | 24 |
| Carbon dots and Derivatives | | Toxicity (CC50) | Antiviral (EC50) | Tested viruses | Tested cell line/inhibition | Year | Ref. |
| Carbon dots | Synthesis from PEG-diamine and ascorbic acid by a process of grounding, autoclaving and purification | >0.250 mg/mL | effective at 0.125 mg/ml only | PRRSV | PK-15 and MARC-145 | 2016 | 63 |
| Boronic acid-tributed carbon quantum dots | Synthesis by calcination of citric acid anhydrous and reaction with 4-carboxy-3- chlorobenzeneboronic acid, 4-dimethylaminopyrid and 1-ethyl-3-(3- dimethylaminopropyl) carbodiimide | >600 μg/ml | 4.69-9.37 μg/ml | HIV-1 | MT-4/HIV-1 and MOLT-4 | 2016 | 61 |
| Functional carbon quantum dots | Synthesis of CQDs-5 and CQDs-6 according to the authors' protocol ¹⁴⁶ | >100 μg/ml (CQDs-5) >100 μg/ml (CQDs-6) | 10-20 μg/ml 2-5 μg/ml | HCoV | Huh-7 | 2019 | 22 |
| Benzoxazine monomer derived carbon dots | Synthesis from benzoxazine monomers and NaOH by an process of autoclaving and purification | >75 μg/ml | JEV 18.63 μg/ml, ZIKV 3.715 μg/ml, DENV 37.49 μg/ml | JEV, ZIKV and DENV | BHK-21 (for JEV) and Vero (for ZIKV and DENV) | 2019 | 147 |
| Glycyrrhizic-acid-based carbon dots | Synthesis from glycyrrhizic acid of Chinese herbal medicine by a hydrothermal method | >0.90 mg/ml | 0.30 mg/ml | PEDV, PRRSV | Vero (for PEDV), MARC-145 (for PRRSV) | 2020 | 54 |
| Graphene and Derivatives | | Toxicity (CC50) | Antiviral (EC50) | Tested viruses | Tested cell line/inhibition | Year | Ref. |
| Graphene | Single layered graphene modeled with the Avogadro software | Not tested | Not tested | HIV-1 | Essential target proteins (HIVVpr, Nef and Gag) | 2014 | 148 |
| Multi-walled carbon nanotubes: Pristine MWCNT (p-MWCNT), ox-MWCNT; CHI360, CHI415 | p-MWCNT produced by catalytic chemical vapor deposition from isobutane on a Fe/Al ₂ O ₃ catalyst and purified (>95%). ox-MWCNT prepared by oxidation of p-MWCNT with nitric acid/sulfuric acid (1:3) | 21.22 μg/ml (p-MWCNT) 11.43 μg/ml (ox-MWCNT) 5.48 μg/ml (CHI360) 75.73 μg/ml (CHI415) | >69.35 μg/ml 9.04 μg/ml 0.01 μg/ml 0.42 μg/ml | HIV-1 | MT-4 | 2015 | 149 |
| Graphene-based materials (GO, rGO, GO/PVP, GO/PDDA, Gt, GtO) | GO from Nanjing XFANO Materials Tech. Gt from Sigma-Aldrich. GtO from Gt via the modified Hummers method. Prepared GO-PDDA, GO-PVP ¹⁵⁰ , and rGO ¹⁵¹ . | >50 μg/ml | PRV effective at 6 mg/ml PEDV effective at 1.5 mg/ml No (GO/PDDA and Gt) | PRV, PEDV | Vero | 2015 | 28 |
| Graphene oxide with silver nanoparticles | GO via Hummers' method and dispersion in a solution with AgNO ₃ and ethylene glycol in microwave oven | 12.5-25 mg/ml | FCoV effective at 0.1 mg/ml IBDV effective at 0.0625 mg/ml | FCoV, IBDV | fcwf-4 | 2016 | 152 |
| Graphene oxide with silver nanoparticles | GO from Chengdu Organic Chemicals and AgNO ₃ from Sigma-Aldrich were self-assembled via interfacial electrostatic force | 8.0 μg/ml | PRRSV effective at 4.0 μg/ml PEDV effective at 2.0 μg/ml | PRRSV, PEDV | MARC-145(for PRRSV) and Vero (for PEDV) | 2018 | 153 |
| Water-soluble GQD and drug-conjugated GQD | Water-soluble GQD prepared by prolonged acidic oxidation of p-MWCNT ¹⁵⁴ . The anchorage of the antiretroviral drugs to the GQD surface by coupling reactions between the nucleophilic amino groups of the drugs and the carboxylic functionalities of the GQD | 62.82 μg/ml (CHI499) 2.71 μg/ml(CDF119) 23.9 μg/ml (GQD-CHI499) | 0.12 μg/ml 0.64 μg/ml 0.066 μg/ml | HIV-1 | MT-4 | 2018 | 155 |
| Graphene platforms with precise dual sulfate/alkyl functionalities | The surface of graphene is functionalized with polyglycerol sulfate (PGS) and aliphatic chains of different length (C ₆ , C ₉ , C ₁₀ , C ₁₁ , C ₁₂) | >1000 μg/ml (G-PGS-C9) 63.4 μg/ml (G-PGS-C10) 68.9 μg/ml (G-PGS-C11) 100.19 μg/ml (G-PGS-C12) | FCoV 749.4 μM, SARS-CoV-2 339.7 μM FCoV 9.8 μM, SARS-CoV-2 29.1 μM FCoV 6.3 μM, SARS-CoV-2 0.8 μM FCoV 8.7 μM, SARS-CoV-2 22.9 μM | FCoV, SARS-CoV-2 | A549, HBE, Vero | 2021 | 156 |

Carbon Dots and Derivatives

Carbon dots (CDs), also known as carbon quantum dots (CQDs) or Cdots, are other members of the CBNs family with small dimensions up to 10 nm in diameter, cost-effective, and environmentally inert.^{23,157} It possesses an organic molecule's chemical functionality, shows a very high surface-to-volume ratio, and can be homogeneously dispersed in water. Many CDs are explored in several fields, such as chemical sensing, bioimaging, electrocatalysis, and other applications.^{62,158} The antiviral activity of functionalized CDs produced from 4-aminophenylboronic acid against human coronavirus (HCoV) infections has been recently demonstrated in human Huh-7 liver cells²² (see Table 1). Benzoxazine monomer-derived carbon dots (BZM-CDs) were effective against the Japanese encephalitis virus (JEV), ZIKV, and DENV.¹⁴⁷ The antiviral activity of highly biocompatible glycyrrhizic-acid-based carbon dots (Gly-CDs) synthesized from glycyrrhizic acid was demonstrated against large-enveloped RNA viruses by using the porcine epidemic diarrhea virus (PEDV) as a viral model of the coronavirus (CoVs).⁵⁴ This virus belongs to the *alphacoronavirus* genus and it cannot be transmitted to humans.¹⁵⁹

Graphene and Related Carbon-Based Nanomaterials

Graphene and its oxidated form, GO, are 2D CBNs with excellent physical and biological properties¹⁶⁰⁻¹⁶⁴ that can be used successfully to detect, and capture viruses^{148,165} (see Table 1). The antiviral activity of carbon nanofibers (CNFs) incorporated into alginate was reported using a non-enveloped double-stranded viral model.¹⁶⁶ However, the antiviral capacity of CNFs has never been tested against an enveloped virus belonging to the same Baltimore group¹⁶⁷ such as SARS-CoV-2. Functionalized multiwall carbon nanotubes (MWCNT), another type of carbon-based filamentous nanomaterials, exhibited potent viral inhibition against HIV.¹⁴⁹ In this study, the effect of hydrophilicity and dispersibility of the nanomaterials showed to be the key to control the antiviral activity of MWCNT-based nanomaterials. Carboxylated MWCNT (ox-MWCNT sample) and drug-conjugated MWCNT (MWCNT-C-CHI36) showed high antiviral activity contrary to pristine MWCNT. GO has also shown potent antiviral activity with nonionic polyvinyl pyrrolidone (PVP) in contrast to its combination with the cationic poly(diallyl dimethyl ammonium chloride) (PDDA).²⁸ The combination of silver nanoparticles (AgNPs) with GO inhibited the infectivity of enveloped feline coronavirus (FCoV) by 25% compared to 16% for GO.¹⁵² AgNPs are well-known alternative antiviral agents that interact with cell surface receptors and blocks of the virus entry into the host cells.⁶⁶ In the same research line, GO-AgNPs nanocomposites showed better viral inhibition capacity than AgNPs or GO using a PRRSV pattern on the replication of virus.¹⁵³ Water-soluble graphene quantum dots (GQD) synthesized from MWCNT through oxidation and exfoliation with and without conjugated antiretroviral agents exhibited efficient viral inhibition of the HIV.¹⁵⁵ Very recently, graphene derivatives with long aliphatic chains have shown inhibition capacity against FCoV and SARS-CoV-2 replication.¹⁵⁶ Therefore, these results confirm the potential utilization of CBNs in the fight against viruses such as SARS-CoV-2.

Carbon-Based Nanomaterials Against Viruses

This current report analyzes the antiviral potentials of CBNs against 13 viruses. The antiviral activities were detected in 40 out of 44 studies as depicted in Figure 4.

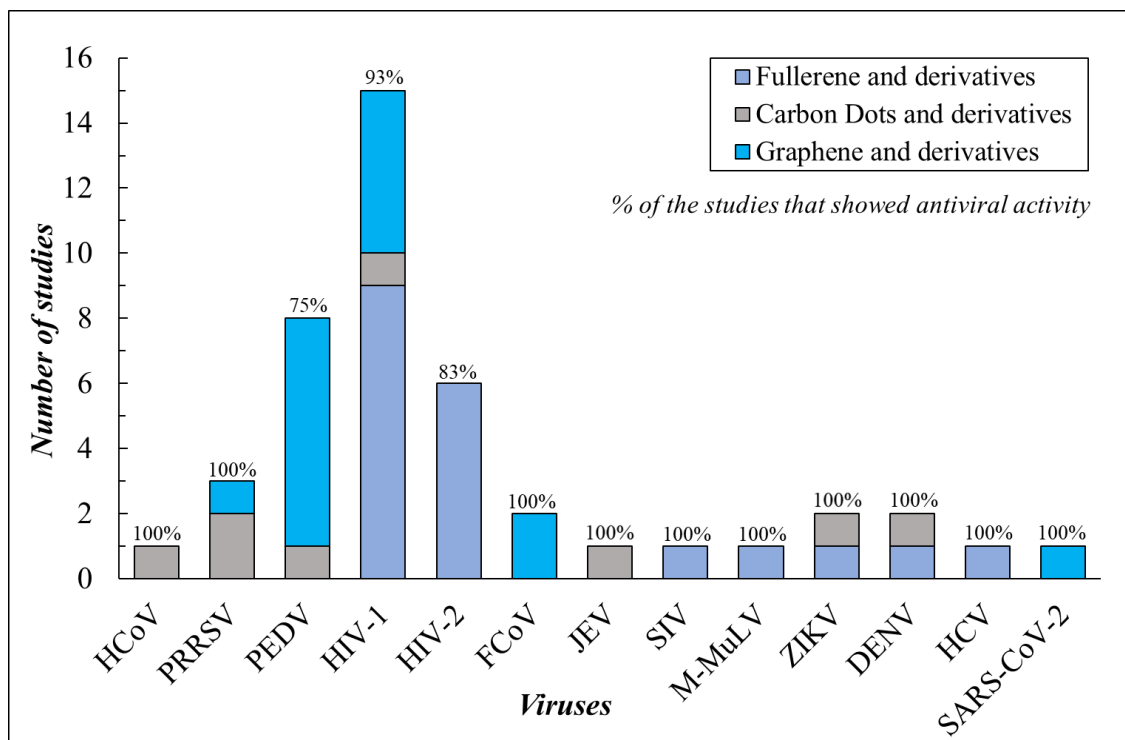


Figure 4. Studies of carbon-based nanomaterials' antiviral activity indicating the percentage of studies that showed antiviral activity against 13 enveloped positive-sense single-stranded RNA viruses. The carbon-based nanomaterials were in the form of fullerenes, carbon dots, graphene and derivatives shown in Table 1.

The number of studies is greater than the 22 published papers shown in Table 1 because several CBNs and/or types of viruses were studied in some publications. To perform this count of studies, only CBNs with different chemical structural forms were considered. Thus, fullerene and its derivatives showed antiviral activity in nine studies against HIV-1,^{26,136,138,140–142,144,145} five studies against HIV-2^{26,140–142,144,145} out of six and against other viruses such as SIV,¹³⁹ M-MuLV,¹³⁹ HCV,¹⁴³ ZIKV²⁴ and DENV.²⁴ Carbon dots and their derivatives exhibited antiviral activity against HCoV,²² HIV-1,⁶¹ JEV,¹⁴⁷ ZIKV,¹⁴⁷ DENV,¹⁴⁷ PEDV⁵⁴ and two studies against PRRSV.^{54,63} Graphene and related CBNs have shown antiviral activity against HIV-1 in four studies out of five,^{148,149,155} five studies against PEDV out of seven,^{28,153} two studies against FCoV^{152,156} and one study against PRRSV¹⁵³ and SARS-CoV-2.¹⁵⁶ All these viruses are enveloped positive-sense single-stranded RNA viruses (IV Baltimore group¹⁶⁷). Therefore, the antiviral properties of CBNs have been tested against a wide range of viruses similar to SARS-CoV-2, which suggests that CBNs are promising nanomaterials as alternative antiviral agents against this pathogen. The viruses tested against the CBNs are shown in Table 2 with all their characteristics such as name, abbreviation, genus, family, viral affection and disease/action and references.

Table 2. Information of the enveloped viruses tested to study the antiviral properties of CBNs belonging to the same Baltimore classification of SARS-CoV-2 (Group IV ((+)ssRNA¹⁶⁷): single-stranded positive-sense RNA virus).

| Virus name | Abbreviation | Genus | Family | Infects | Disease/action | References |
|---|--------------|------------------|---------------|--|---|-------------------------------|
| Human coronavirus | HCoV | Alphacoronavirus | Coronaviridae | Humans | Common cold, pneumonia and bronchiolitis | 22 |
| Porcine reproductive and respiratory syndrome virus | PRRSV | Betaarterivirus | Arteriviridae | Pigs | Porcine reproductive and respiratory syndrome | 54,63,153 |
| Porcine epidemic diarrhea virus | PEDV | Aphacoronavirus | Coronaviridae | Pigs | Porcine diarrhea | 28,54,153 |
| Human immunodeficiency virus type 1 | HIV-1 | Lentivirus | Retroviridae | Humans | AIDS | 26,61,136,140–142,148,149,155 |
| Human immunodeficiency virus type 2 | HIV-2 | Lentivirus | Retroviridae | Humans | AIDS | 26,140–142 |
| Feline coronavirus | FCoV | Alphacoronavirus | Coronaviridae | Cats | Feline infectious peritonitis | 152,156 |
| Japanese encephalitis virus | JEV | Flavivirus | Flaviviridae | Humans through <i>Culex</i> mosquitoes | Inflammation of the brain occurs | 147 |
| Simian immunodeficiency virus | SIV | Lentivirus | Retroviridae | Non-human primates | Simian AIDS | 139 |
| Moloney murine leukemia virus | M-MuLV | Gammaretrovirus | Retroviridae | Mouse | Cancer | 139 |
| Zika virus | ZIKV | Flavivirus | Flaviviridae | Humans through <i>Aedes</i> mosquitoes | Zika fever | 24,147 |
| Dengue virus | DENV | Flavivirus | Flaviviridae | Humans through <i>Aedes</i> mosquitoes | Dengue fever | 24,147 |
| Hepatitis C virus | HCV | Hepacivirus | Flaviviridae | Humans | Hepatitis C | 143 |
| Severe acute respiratory syndrome coronavirus 2 | SARS-CoV-2 | Betacoronavirus | Coronaviridae | Humans | COVID-19 | 156 |

Mechanism of Action of CBNs against Viral Infection

The antiviral mechanisms of fullerenes, carbon dots, graphene and related carbon-nanomaterials are still not completely understood. However, some progress in understanding the mechanism of action of these promising antiviral agents has been achieved. Details of these suggested mechanisms are discussed below.

Fullerene and Derivatives

Antiviral fullerene derivatives can inhibit viral entry, modify its morphology and functions, and block viral replication.³⁰ Studies about the antiviral mechanism of action of C₆₀-fullerene derivatives against viruses such as HIV-1 and HIV-2 suggest that the C₆₀ carbon sphere fits well to the active site of some HIV enzymes such as the HIV-protease.^{136,138,144} In the same research line, a diamido diacid diphenyl fulleroid derivative (2c) was found to be an inhibitor of HIV-1 and HIV-2 protease and reverse transcriptase at low micromolar concentration.¹⁴⁴ More recently, the series of fullerene derivatives shown in Figure 3 exhibited potential inhibition of hepatitis C virus (HCV) NS5B polymerase and HCV NS3/4 protease.¹⁴³ On the other hand, the mechanism of aqueous fullerene preparations of C₆₀-fullerene combined with PVP (C₆₀/PVP) against influenza A virus has been reported.¹⁶⁸ Influenza A virus is a negative-sense single-stranded virus that belongs to the Baltimore group V.¹⁶⁷ However, it is an enveloped RNA virus like SARS-CoV-2. The antiviral mechanism of action of the C₆₀/PVP complexes are attributed mainly to the lipid component of virus membranes as a membranotropic agent.¹⁶⁸ Thus, the round and oval morphology of the viral particles before being in contact with the C₆₀/PVP preparation was observed by transmission electron microscopy. The well-defined surface glycoproteins in the form of "brush" lost their integrity of viral envelopes when they were in contact with the C₆₀/PVP complexes by breaking the lipoprotein envelope structure and these complexes fused with the virion-like aggregates.

Carbon Dots and Derivatives

In the context of antiviral mechanisms, CDs could inhibit viral replication by activating the interferon response for the porcine reproductive and respiratory syndrome virus (PRRSV).⁶³ Furthermore, CDs conjugated with carboxyl phenylboronic acid (CBBA) prevented the entry of HIV-1 viruses into cells by suppressing syncytium (Figure 5).⁶¹

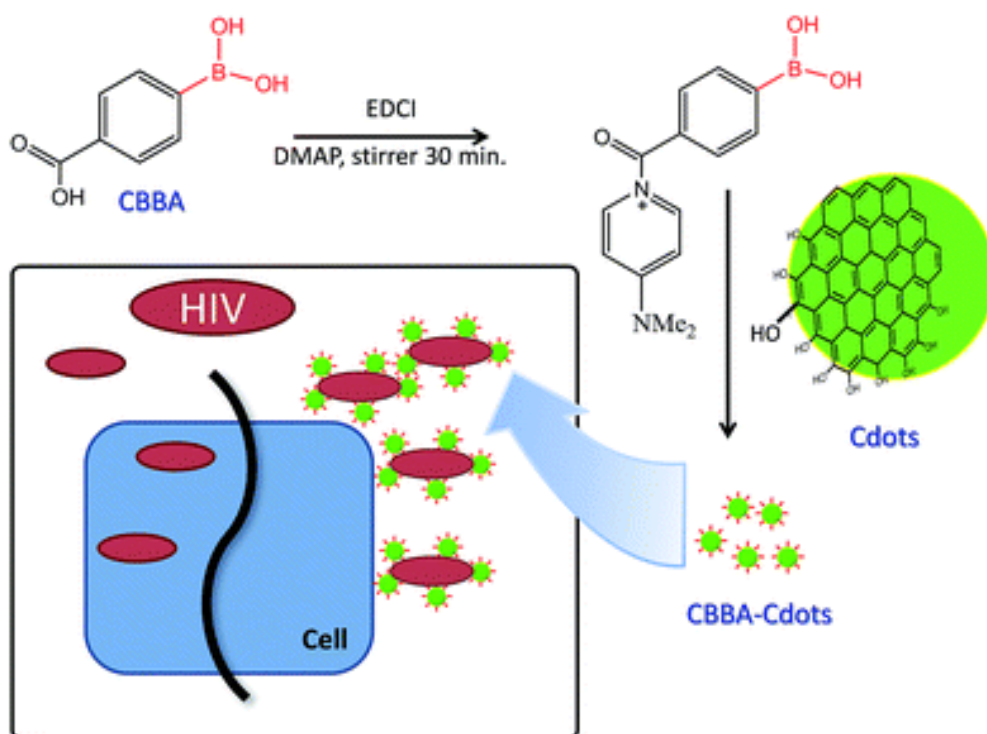


Figure 5. Schematic illustration of conjugating carboxyl phenylboronic acid (CBBA) on Cdots (CBBA-Cdots) and different mechanisms of inhibition entry - *Published by The (RSC)*. Reprinted with permission from ref 61. Copyright 2016 Royal Society of Chemistry.

The antiviral studies of functionalized CDs produced from 4-aminophenylboronic acid against human coronavirus (HCoV) infections in human Huh-7 liver cells showed inhibition of the viral entry and effects at the replication steps which was ascribed to the interaction of the CBNs' functional groups with the viral entry receptor DPP4²² (see Figure 6).

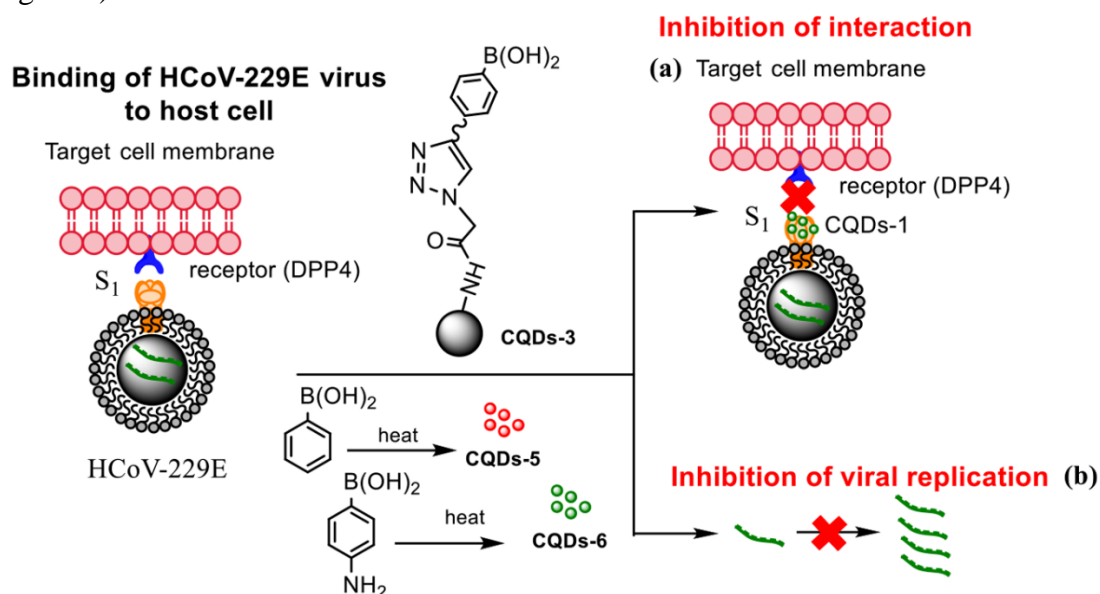


Figure 6. Influence of carbon quantum dots (CQDs) on the binding of HCoV229E virus to cells: (a) inhibition of protein S receptor interaction (b) inhibition of viral replication. Reprinted with permission from ref 22. Copyright 2019 American Chemical Society.

Graphene and Related Carbon-Based Nanomaterials

Graphene and GO can destroy the virus surface proteins, and extract their RNA by bioreduction.¹⁶⁵ The high binding affinity of graphene to the essential target proteins HIV Vpr, Nef, and Gag during HIV infections was reported in 2014.¹⁴⁸ Evaluation of the antiviral capacity of GO and rGO against PEDV showed significant viral inhibition by inactivating the virus before entering the cell (Figure 7).²⁸

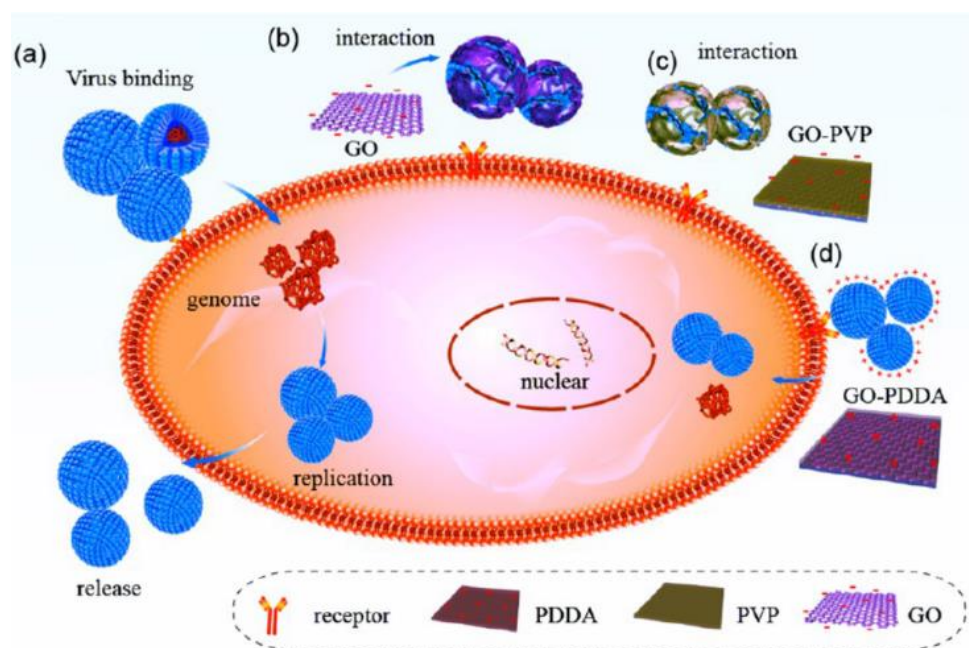


Figure 7. Possible antiviral mechanisms of graphene oxide (GO): (a) Infection initiation: virus binding by interaction with cell receptors; (b) Interaction of negatively charged GO nanosheet with the positively charged viruses, producing virus damage and infection inhibition; (c) GO conjugated with nonionic PVP blocked infection but GO with cationic PDDA did not (d). Reprinted with permission from ref 28. Copyright 2015 American Chemical Society.

It was reported that, the sharp edges of the GO or rGO nanosheet inactivated the virus by physical disruption of its biological structure through direct interaction which resulted in the outflow of intracellular metabolites.²⁸ Since rGO and GO exhibited a similar viral inhibition capacity in that study, the surface functional groups present in these CBNs may play a minor role. The antiviral activity was concentration and time-dependent incubation. Therefore, the potent antiviral activity of both GO and rGO can be attributed to the negative charge, which favors the electrostatic interaction with the positive charge of the virus and the single nanosheet-layer structure.³⁰ On the other hand, graphite (Gt) showed no viral inhibition and graphite oxide (GtO) exhibited weaker viral inhibition than monolayer GO and rGO, suggesting that the nanosheet form plays a significant role in the antiviral activity.²⁸ In the same research line, GO-AgNPs nanocomposites prevented PRRSV from entering the host cells (~59.2% inhibition) and improved the production of interferon- α (IFN- α) and ISGs, which directly block the proliferation of PRRSV.¹⁵³ Furthermore, graphene sheets with defined dual sulfate/alkyl functionalities have shown potent antiviral activity against FCoV and SARS-CoV-2.¹⁵⁶ Here, graphene

acted as a 2D platform to allow the interaction of the negatively charged polyglycerol sulfate (PGS) branches with the positively charged patches of the virus particles, and then the long aliphatic chains (C11) ruptured the membrane of the lipid envelop. Thus, G-PGS-C11 displayed the strongest antiviral activity against SARS-CoV-2 without exhibiting significant toxicity against eukaryotic host cells (Figure 8).

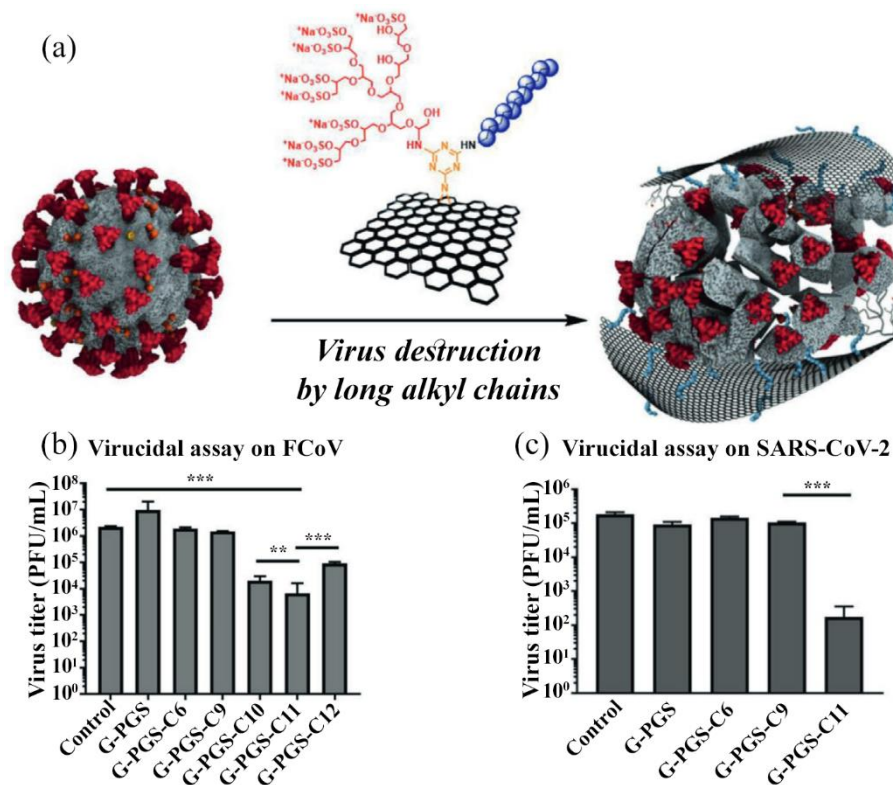


Figure 8. Schematic representation of virus rupturing by G-PGS-C11(a). Virucidal assays for the functionalized graphene platforms against FCoV (b) and SARS-CoV-2 (c). Values are expressed as mean \pm standard deviation ($n = 4$). Adapted with permission under a Creative Commons CC BY 4.0 License from ref 156. Copyright 2021 Wiley-VCH GmbH.

Carbon-based nanomaterials may exercise multiple mechanisms against positive-sense single-stranded RNA viruses according to their physical configuration, chemical modifications, and metabolism. Hence, CBNs could work directly against the virus particle by distorting the envelope or the capsid organization; additionally, they may exert a steric hindrance effect by physically occupying a catalytic site of an essential viral enzyme or a receptor cavity.¹³⁷ When chemically modified with charged residues or metabolically activated, CBNs could perform both a direct disrupting effect on the virion structure and an indirect antiviral activity due to tuning of the redox signaling and the homeostatic innate/inflammatory response of the target cells.³⁰ All of the above functions, coupled with a negligible toxicity, may account for the anti-SARS-CoV-2 therapeutic potential of carbon compounds.¹⁵⁶ An even synergistically increased inhibitory effect may be played by CBNs when loaded with specific antiviral drugs.³⁰ Thus, the direct and intrinsic antiviral activities of the compounds plus the loaded antiviral drug will work synergistically against the viral particles which may increase the viral destruction potential.¹⁶⁹ Another characteristic feature of the CBNs is based on the immunostimulatory potentials,^{170,171} which will derive and propagate the antiviral cell-mediated immunity, which also works synergistically with the CBNs-drug leading to

increase the virally infected cells and/or viral particle accessibility for CBN's or CBNs-drug achieving a more efficient viral infection clearance (Figure 9) through many suggested scenarios.¹⁷²

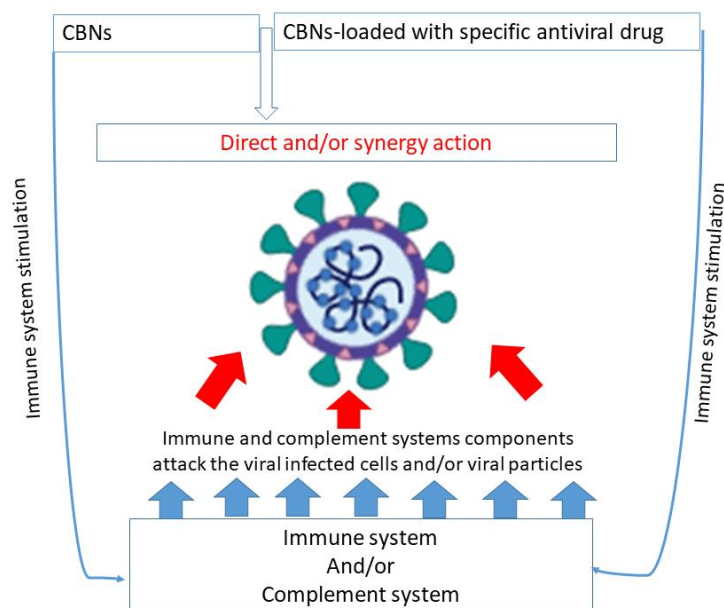


Figure 9. The suggested mechanism of action of CBNs against viral infection. The CBNs could work against viral and secondary infection in three scenarios, 1. CBNs alone or 2. in synergism with loaded antiviral drugs 3. and/or in synergism with the immune system components depending on the CBN's immunostimulatory potentials.

The most versatile interesting feature of CBNs is selecting one or more entities of them and functionalizing the selection base on the target function. The planning interactions between empty or loaded CBNs and the immune system, including the complement system, can be reciprocal in the context which immune system components would involve.^{172,173}

Toxicological Aspects of Carbon-Based Nanomaterials

There are widespread concerns on the toxicological aspects of CBNs because some studies have reported that depending on the type of CBNs, dimensions, oxidation degree, functionalization, concentration, and exposure time, CBNs may exert cytotoxicity effects on host cells.^{95–102} Nevertheless, we focused our attention on the toxicological studies performed with the CBNs tested against the 13 enveloped single-stranded positive-sense RNA viruses analyzed in this review (Table 1). Details of these studies are discussed below.

Fullerene and Derivatives

An anti- HIV-1 fullerene derivative (compound 1) showed no cytotoxicity on human PBM cells in 1993.¹³⁶ Another study reported non-cytotoxicity for concentrations up to 100 μM of an anti-HIV bis(monosuccinimide) derivative of p,p'-bis(2-aminoethyl)diphenyl- C_{60} in peripheral blood mononuclear (PBM) cells and H9 human embryonic stem cells, Vero, and CEM cells.¹⁴⁵ In 1996, nine anti-HIV functional derivatives of C_{60} -fullerene showed no cytotoxicity for concentrations also up to 100 μM . However, a series of anti-HIV-1 bis-functionalized fullerene derivatives were

developed after that in 2003 and only one of them (derivative 1) exhibited moderate toxicity.¹⁴⁰ Nonetheless, low cytotoxic properties were reported for anti-HIV cationic fullerene derivatives and anti-HIV water-soluble fullerene derivatives in 2005 and 2007, respectively.^{141,142} A later study in 2011 showed that anti-HIV derivatives of C₇₀-fullerene also exhibited low toxicity *in vitro* and *in vivo*.²⁶ More recently, an anti-HCV fullerene derivative (derivative 1a, Figure 3) showed no cytotoxicity in the low micromolar range.²⁵ Furthermore, very recently, anti-ZIKV and anti-DENV tridecafullerenes appended with up to 360 1,2- mannobiose showed no cytotoxicity in the picomolar range.²⁴

Carbon Dots and Derivatives

CDs are highly promising nanomedicine tools for antiviral applications due to their low toxicity and potent antiviral activity.¹⁵⁸ Thus, CDs showed antiviral activity against PRRSV and low cytotoxicity in MARC-145 cells.⁶³ Furthermore, the modified CDs or their combination with other compounds significantly decreased the cytotoxicity of these carbon-based antiviral nanomaterials.^{22,54,61,147} For example, in the cytotoxicity tests of both Cdots and CBBA-Cdots at high concentrations (up to 300 mg·mL⁻¹), the proliferation of human cells was as fast as that of the untreated cells (control) after 24 hours incubation suggesting the absence of cytotoxic effects for both types of nanomaterials.⁶¹ However, this study did not assess ROS or cytokine generation. Immunomodulatory effects are known to be induced by other carbon-based nanoparticles such as graphene (see the next paragraph). Anti-HCoV CDs produced from 4-aminophenylboronic acid, BZM-CDs with anti-JEV, anti-ZIKV and anti-DENV properties, and anti-PEDV and anti-PRRSV Gly-CDs manifested no cytotoxicity.^{22,54,147}

Graphene and Related Carbon-Based Nanomaterials

The toxicological analysis of pristine MWCNT, ox-MWCNT and MWCNT-C-CHI36 with anti-HIV-1 properties showed opposite results.¹⁴⁹ Thus, ox-MWCNT and MWCNT-C-CHI36 showed low cytotoxicity contrary to pristine MWCNT which exhibited high cytotoxicity. However, GO showed potent anti-PEDV using a non-cytotoxic concentration ($\leq 6 \mu\text{g/mL}$).²⁸ Anti-FCoV GO-AgNPs nanocomposites and neat GO could also be prepared at very low or non-cytotoxic concentrations.¹⁵² In the same way, anti-PRRSV GO-AgNPs nanocomposites could be prepared at a non-cytotoxic concentration ($\leq 4 \mu\text{g/mL}$).¹⁵³ Finally, a water-soluble GQD with a conjugated antiretroviral agent (GQD-CHI499) was selected as an excellent potential candidate due to its high antiviral activity against HIV and low cytotoxicity.¹⁵⁵ Anti-FCoV and anti-SARS-CoV-2 graphene platforms have shown a large concentration window without significant toxicity against human cells.¹⁵⁶ Therefore, the lack of toxicity could provide great potential in the development of safe therapeutics based on carbon-based nanomaterials to combat COVID-19 in the microbial resistant era.

Conclusions

Carbon-based nanomaterials have been evaluated for their antiviral activity against 13 enveloped viruses (HCoV, PRRSV, PEDV, HIV-1, HIV-2, FCoV, JEV, SIV, M-MuLV, ZIKV, DENV, HCV and SARS-CoV-2), all single-stranded positive-sense RNA viruses belonging to the Baltimore group IV. Most of the studies have shown a potent antiviral activity and from low to no toxicity supporting the potential for the use of CBNs to

1
2
3 combat SARS-CoV-2. As a revolutionary technology approach to treat COVID-19, these
4 carbon-based therapeutics can provide a significant breakthrough as these nanomaterials
5 allow the targeting of microbial resistance issues and can potentially induce tissue
6 regeneration at the same time. Furthermore, these antimicrobial nanoweapons could be
7 employed to deal with SARS-CoV-2 alone or with other types of viruses, bacteria, or
8 fungi, causing pneumonia, including multidrug-resistant strains. The chance of success
9 applying these wide-spectrum antimicrobial nanomaterials is very high because of the
10 preliminary antiviral results reported for 13 viruses and the fact that the proposed
11 approach could be extended to other types of pneumonia caused by other important
12 pathogens.
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Author Contributions

ÁSA conceived the idea of this work, wrote the draft manuscript and major editing. KT, ATM, MS, VNU, KL, PA, AAAA, GC, RK, AL, BDU, DB, EMR, NGB, and YKM edited the manuscript, and SSH, PPC, GP, MMT, TMAEA, SS, and AMB proof-read the manuscript.

Competing interests

The authors do not have any conflicts of interest to declare.

Vocabulary

Coronavirus disease 2019 (COVID-19), viral infectious disease that has spread throughout the world causing the current COVID-19 pandemic; **Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)** is the causative pathogen responsible for the COVID-19 disease; **Carbon-based nanomaterials (CBNs)** are materials mainly constituted by carbon atoms that possess a broad range of antimicrobial properties; **Enveloped positive-sense single-stranded RNA viruses** are viruses that belong to the IV Baltimore group similar to SARS-CoV-2; **Pneumonia** is an infection of the lungs caused by bacteria, viruses or fungi.

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