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Antiviral Coating for Mitigation of COVID-19 Pandemic: A Review on the Role of Nanomaterial for Safer Surface against COVID-19

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ABSTRACT

The COVID-19 pandemic the world has been facing is caused by the novel coronavirus, SARS-CoV-2. The virus can remain on certain surfaces for an extended period. As a consequence, contact with the surfaces can cause a healthy human to contract the disease. Although certain household items work against contaminated surfaces, none of the disinfectants can be used for a considerable amount of time. Therefore, the assessment and use of non-corrosive and non-toxic disinfectants are critical to stop the infection from spreading. Copper, along with its compounds and polymers, CPEs and OPEs, and Carbon Nanomaterials have demonstrated effective antibacterial and antiviral activity against bacteria such as E. Coli, S. Aureus, and viruses such as Influenza A virus. This review investigates the potential of using these substances as a surface coating to render the SARS-CoV-2 virus inactive. In addition, the review summarizes helpful information regarding the antimicrobial and antiviral activity and mechanism of polymers, copper, and carbon nanostructures. It also discusses the efficacy of these functional coatings in deactivating the SARS-CoV-2 virus.

Keywords: *antiviral coating, covid-19*

1. INTRODUCTION

In late 2019, an outbreak of a new coronavirus occurred in Wuhan, China, which is an emerging business hub. The virus, known as Severe Acute Respiratory Syndrome 2 (SARS-CoV-2), is responsible for causing Coronavirus Disease 2019 (COVID-19) [1]. On March 11, 2020, the World Health Organization (WHO) declared COVID-19 as a pandemic [2]. Coronaviruses are a type of RNA virus with a positive-sense single-stranded RNA. They belong to the *Coronaviridae* virus family, which includes α, β, γ, and δ coronaviruses [3]. Specifically, the coronavirus responsible for COVID-19 is identified as β-coronavirus [4]. Although COVID-19 has a strong infection capability, its morbidity and mortality rates are lower compared to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) [5].

The primary mode of transmission for this β-coronavirus is via direct contact with respiratory droplets, or aerosols from an infected person. These aerosols can enter the lungs when inhaled through the nose or mouth [1]. Additionally, the virus can spread when a person comes into contact with virus-contaminated objects or surfaces, especially those used by infected individuals [6].

The virus can survive on surfaces for a certain period, making it crucial to inactivate the virus on surfaces to reduce transmission.

Recent research has focused on developing coatings for solid surfaces that can quickly and efficiently inactivate the SARS-CoV-2 virus. It is important for these surface coatings to be mechanically strong and maintain their effectiveness against the virus [7]. While conventional disinfectants like bleach, hydrogen peroxide, and alcohol solutions are effective against SARS-CoV-2 [8], their volatile and corrosive nature limits their ability to provide prolonged sterilization [9].

To address this, scientists have investigated various substances with antimicrobial properties that could serve as effective disinfectants against COVID-19. These include polymers, conjugated polyelectrolytes (CPEs), oligomeric phenylene ethynylenes (OPEs), copper oxide particles, and carbon-based nanomaterials. Polymers, CPEs, and OPEs have shown antimicrobial activity under both light-irradiated and dark conditions, with minimal cytotoxicity to mammalian cells at low concentrations [10][11]. Copper

oxide particles incorporated into thin polyurethane (PU) films have demonstrated the ability to deactivate the virus by 99.99% within 1 hour [7]. Carbon-based nanomaterials possess strong antimicrobial activity, biocompatibility, and biodegradability, making them promising candidates against the SARS-CoV-2 virus and other microorganisms, including drug -resistant strains [12].

The objective of this review is to examine the antimicrobial properties of copper oxide, polymers, CPEs, OPEs, and carbon nanomaterials, and to assess their feasibility as disinfectants against COVID-19. Additionally, the review aims to evaluate the cytotoxicity associated with these substances and identify future research directions in this field.

2. STABILITY OF SARS-COV-2 ON SURFACE

SARS-CoV-2 has high stability at low temperatures of 4°C. However, the virus is highly sensitive to heat and inactivates within 5 minutes at high temperatures of 70°C. The virus has high stability at room temperature at a pH of 3 to 10 [14]. SARS-CoV-2 is highly stable on plastic and stainless-steel surfaces. On these surfaces, the virus can be detected even after72 hours. However, there is a high virus titer depletion from $10^{3.7}$ to $10^{0.6}$ $TCID_{50}$ per milliliter of a plastic medium after 72 hours and $10^{3.7}$ to $10^{0.6}$ $TCID_{50}$ per milliliter of stainless-steel medium after 48 hours. No SARS-CoV-2 is detected on copper surfaces after an incubation period of 4 hours [15].

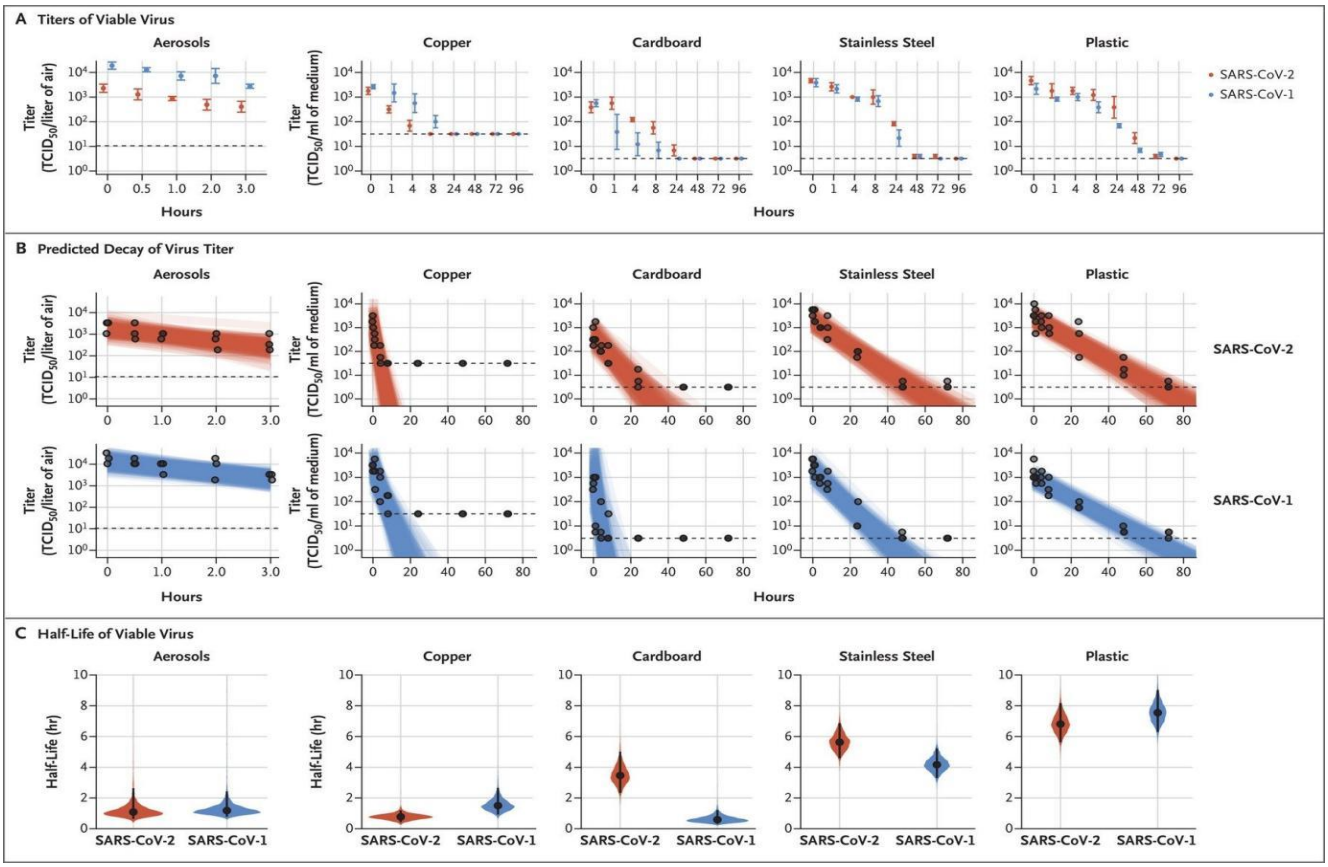

Figure 1 Surface stability of the two coronaviruses - SARS-CoV-1 and SARS-CoV-2 in different surfaces [10]

The stability of SARS-CoV-2 on cardboard is low, and no virus is detected after 24 hours [15]. No virus can be detected on paper or tissue after a 3-hour incubation period. For clothes and wood, after an incubation period of 2 days, no virus can be detected on the surface [14].

3. COPPER AS AN ANTIVIRAL AND ANTIMICROBIAL AGENT

3.1 Antimicrobial and Antiviral Mechanism of Copper

Copper and its compounds employ a mechanism called "contact killing" to kill bacteria and viruses on their surfaces. Contact killing on copper surfaces takes place at a rate of 7 to 8 logs per hour. With prolonged incubation, all microorganisms present on the surface of copper are killed [16]. Copper ions are released when copper and copper alloys are in the aqueous phase as a primary toxicity mechanism. Bacteria in contact with the copper surface are starved for nutrients which disables bacterial growth and eventually kills them [17]. There is extensive membrane damage in cells when exposed to copper, which contributes to contact killing. It is also proven that mutative genotoxicity and deoxyribonucleic acid (DNA) abrasions are not the antimicrobial mechanisms employed by dry metallic copper [18]. A series of actions are responsible for bacterial killing, starting with the copper intruding into the cells following membrane damage, and then oxidative stress damaging the DNA [19]. However, in a study by Warnes and Keevil, it was shown that copper-

induced antibacterial activity does not cause cell damage. An alternative method of direct or indirect action by ionic copper substances and superoxide generation was proposed, which results in arrested respiration and DNA failure, causing cell death [20].

Copper exhibits biocidal activity through various mechanisms. Firstly, it binds and disarranges helical structures by cross-linking within and between nucleic acid strands, leading to the denaturation of nucleic acids. Secondly, it alters proteins and hinders their normal biological assembly and activity. Additionally, copper can puncture the plasma membrane, causing damage to the outer protective layer of microorganisms. Lastly, peroxidation takes place between membrane lipids and Reactive Oxygen Species (ROS), resulting in oxidative damage. These combined mechanisms contribute to the biocidal effects of copper [21].

3.2 Antimicrobial Activity of Copper

Copper compounds can halt both Gram-negative and Gram-positive bacteria. Solid-state cuprous compounds are found to be more efficient in deactivating bacteria and viruses than cupric and silver compounds. When copper compounds were incubated with bacteriophage Qβ, there were significant log reductions for Copper (I) Oxide (Cu_2O), whereas Copper (II) Oxide (CuO) showed negligible changes [22]. Viability tests performed with copper alloys and *E. hirae* bacteria showed that Cu_2O exhibited similar antibacterial activity as pure copper. However, Cupric Oxide showed reduced antimicrobial activity, with 10^3 bacteria cells present after 300 minutes of incubation [23]. Cu^+ is more toxic than Cu^{2+} and, therefore, more effective at inactivating bacteria [24]. Copper coupons of 99% Cu and 63% Cu were tested against Gram-negative bacteria *E. coli, Enterobacter spp., P. aeruginosa, A. baumannii,* and *Klebsiella pneumoniae.* Copper surfaces are capable of exhibiting toxicity against all tested bacteria strains. 99% copper coupons had a fast response to the bacteria, with bactericidal effect taking place within 2h, 3h, 5h, and 6h for *A. baumannii, Enterobacter spp., K. pneumoniae, and, P. aeruginosa* and *E. coli* subsequently [25].

The minimum concentration of copper needed for a surface to be an efficient antimicrobial agent is 55% for bacteria. The antimicrobial activity of copper increases proportionally with the concentration of copper present on a surface [26]. Pure copper exhibits higher antimicrobial activity [27]. The temperature influences the rate of antimicrobial activity on copper surfaces. Copper alloys Cu11000 and Cu70600 tested against *P. aeruginosa* PAO1 and *P. aeruginosa* cinR::ISIacZ/hah at 4°C can last for a long time. The killing of bacteria is therefore more effective and rapid at higher temperatures [28].

Copper-silver (CuAg) alloys with 10 wt% of silver showed a substantial increase in antimicrobial activity compared to the pure elements. The CuAg alloy in bulk aqueous phase resulted in a high concentration of copper ions of 568 ± 18 $\mu molL^{-1}$ and a silver ion concentration of less than 0.2 $\mu molL^{-1}$ after 100 mins. The ionic concentration of copper is higher than that of pure copper and is accountable for the increased microbial activity [29].

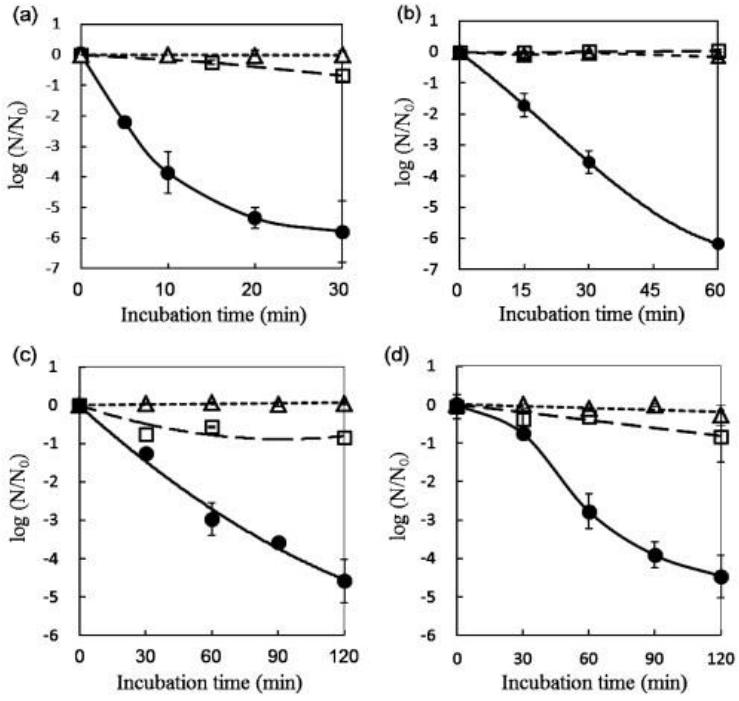

Figure 2 Inactivation of bacteriophage – (a) Qβ (b) T4 (c) *E. coli*, and (d) *S. aureus* by inoculation of the cells on glass substrates filled with Copper (I) Oxide (filled circles), Copper (II) Oxide (open circles), and Silver (squares). The particles were loaded in 2.1 μmol of copper and 2.1 μmol of silver. [27]

3.3 Antiviral Activity of Copper

Copper can be used to inactivate viruses as well. Cuprous Oxide Nanoparticles (CO-NPs) at low concentrations of 0.5 to 8 µg/ml, which is considered to be non-cytotoxic, can exhibit substantial antiviral inhibitory effects on the Hepatitis C Virus (HCV). CO-NPs can block virus infection at both entry and attachment levels. When added to HCV at the attachment step at 4°C and the temperature shift, CO-NPs showed viral activity inhibition [30].

$2x10^6$ particles of Influenza A virus were inoculated and then incubated on a copper surface at a temperature of 22°C and 50 to 60% relative humidity. After a 6-hour incubation period, only 500 particles were active. There is rapid virus inactivation on copper surfaces [31]. Herpes Simplex Virus (HSV) tested with 100 to 200 mg of Cu(II) per liter showed virus inactivation. 90% of HSV was inactivated after only 30 minutes [32]. CuI nanoparticles of an average size of 160nm capable of inactivating influenza virus; EC_{50} was 0.0017% after one hour of treatment. CuI exists as Cu^+ in an aqueous solution, and the ion is involved in ·OH generation. ·OH is a Reactive Oxygen Species (ROS) that uses the oxidation process to bring about damage in biological tissues and cells [33].

Copper alloys containing 79 to 89% copper were tested against Murine Norovirus (MNV-1). There was rapid inactivation of the virus. However, the efficiency was reduced for 70% of copper alloys. This suggests that copper concentration affects antiviral activity [34].

3.4 Cytotoxicity of Copper and its Compounds

Although copper oxide was found to be safe to be used on skin, copper and its compounds were found to be cytotoxic to mammalian cells in some studies. Copper nanoparticles exposed on 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay on THP-I cells for one day exhibited the greatest toxicity among other metal nanoparticles. The Toxic Concentration 50 (TC50) value was below 15 µg/ml [35]. Copper ions are more toxic than copper nanoparticles (NPs) against all cells apart from mammalian cells and yeast. Copper NPs were more toxic to aquatic organisms than bacteria, with median MIC values for bacteria of 200 mg/L. The value of L(E)C50 for mammalian cells was 25 mg/L [36]. Copper is poisonous to algae and mollusks and is only suitable for seawater [37]. $CuCl_2$ was found to be more toxic than CU_2O NP when 96h LC50 values were compared. When exposed to CU_2O NP, Zebrafish larvae (ZFL) accumulate copper at a greater rate compared to $CuCl_2$ but the accumulation of copper is almost similar for ZFL [38]. CuO tested against HEp-2 cells decreased the cell viability of cells, with maximum cell death occurring after 5 hours of treatment. It was proposed that the copper oxide particles induced cellular damage through oxidative stress. Thus, there is a risk of pulmonary and respiratory diseases in humans if exposed to CuO nanoparticles [39]. In a study done by Borkow G., copper oxides did not show any adverse effects when exposed to skin, confirming the safety of oxides of copper being used in commercial products with possible dermal contact.

Table 1. Safety studies performed with Copper Oxide products [40]

Procedure	Type of study	Copper oxide loading (% w/w)	Outcome
Nonclinical	Rabbit skin irritation test	0.4-3.0%	No skin irritation
	Guinea-pig maximization test	0.4	No allergenicity
	Porcine partial thickness wound test	2.3	Normal erythema, edema, and crust formation. Normal clinical pathology and wound healing
	Diabetic mice wound model	2.3	No adverse reaction, or precancerous change of atypia. Boost wound healing
	Elution safety studies	3.0	Copper levels cluting through air or saliva -safe
Clinical trials	Hands skin	1	No irritation or adverse reactions
	Facial skin	0.8-1.0	No irritation or adverse reactions
	Foot skin	0.5	No irritation or adverse reactions
	Thigh skin	1	No irritation or adverse reactions

3.5 Microbial Resistance to Copper

Copper, copper compounds, metal oxides, and nanoparticles are used to investigate the resistance mechanisms developed by microbes against toxic metals Specifically, copper resistance has been observed in plant pathogenic strains of *P. syringae* when subjected to a significant amount of copper compounds. Blue Cu^{2+} ions were accumulated by the bacteria in the periplasm and outer membrane [42]. To detoxify cytoplasmic copper, encoding of Cu^+-ATPase is done by genomes of Gram-negative bacteria. ATPases ensure the bacteria survive in the host organism. Studies have shown that copies of Cu^+-ATPase are present in genomes of both pathogenic and symbiotic bacteria [43]. Two homologous Cu^+-ATPase CopA1 and CopA2 were found in *P. aeruginosa* [44].

Bacteria extracted from copper alloy coins were found to be resistant to the toxicity exercised by copper metal with Gram-positive staphylococci and micrococci, *Kocuria palustris*, and *Brachybacterium conglomeratum* being the most resistant [45]. Copper resistance has also been reported to be plasmid-encoded in *E. coli, Proteus vulgaris*, and *P. syringae* isolates [46].

4. POLYMERS AS AN ANTIVIRAL AND ANTIMICROBIAL AGENT

The use of effective and specific biocidal and virucidal systems holds great potential in alleviating, fighting, and eliminating bacterial and viral infections. Polymers play a crucial role in this regard, as they are deposited on surfaces to combat pathogens, leveraging their intrinsic properties [47]. These polymers, when in contact with microorganisms, can penetrate their membranes, leading to membrane rupture and eventual cell death. However, a specific thermodynamic issue related to polymer chains can be addressed by making the polymer chains cationic [48]. By imparting a positive charge to the polymer coating, the chains can remain separated from the surface and stand upright. The electrostatic attraction takes place when the negatively charged surface of the microorganism and the positively charged polymer coating attract each other, which ultimately results in the rupturing of the microbe's cell envelope and its demise [49].

4.1 Antimicrobial and Antiviral Properties of Polymeric Coatings

To effectively kill airborne and waterborne bacteria, long, hydrophobic, and synthetic polycations can be attached covalently to various surfaces like glass, plastics, and textiles [50]. For instance, a dry -state glass surface coated by hexyl-PVP demonstrates the ability to eliminate over ninety percent of S. aureus bacterial cells, as well as a significant reduction in S. epidermidis, P. aeruginosa, and E. coli bacteria [51]. Another approach involves the covalent bonding of a positively charged ionic polymer, polyallylamine, with glass surfaces (GOPTS/PA), which has shown effectiveness against Gram-positive bacteria S. epidermidis and S. aureus, resulting in a 97% kill rate. However, its efficiency is slightly reduced against Gram-negative bacteria, such as P. aeruginosa, achieving an 88% killing efficiency [52].

An alternative technique for forming films on surfaces is Layer-by-layer (Lbl) electrostatic technology, which involves modifying polymers with hydrogen-bond donor and acceptor groups. This allows the construction of films containing various functional groups of polymers, leading to thin films with antibacterial and virucidal properties [53]. Lbl films created using N, N-dodecyl, methyl-polyethyleneimine (a polycation), and a polyanion have demonstrated efficacy as opposed to Gram-positive S. aureus bacteria, Gram-negative E. coli bacteria, and influenza viruses. Increasing the number of bilayers further enhances the antibacterial and virucidal activities, with 100% bacterial activity achieved using 14.5 bilayers of $(DMLPEI/PAA)_n$ at pH 5 [54]. Moreover, these polymeric coatings also exhibit effectiveness against viruses. For instance, a glass slide coated with branched N, N-dodecyl methyl-PEI demonstrated a reduction in virus titer by 4 logs in 30 minutes when exposed to influenza virus [55].

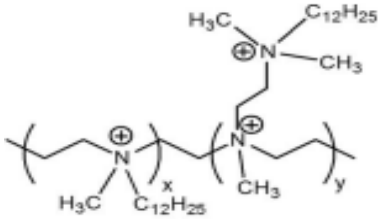

Figure 3. Chemical structures of N, N-dodecyl methyl-PEI [55]

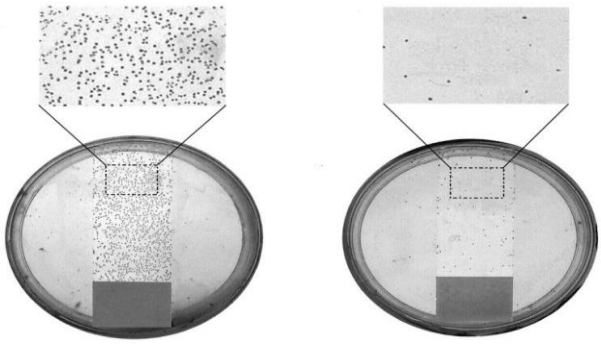

Figure 4. Photographs of S. aureus bacteria in aqueous suspensions sprayed, dried in air for two minutes, and cultured under 0.7% agar in growth medium at 37°C overnight on a regular commercial NH2 glass slide photograph (left) and a hexyl-PVP-modified slide (right) [51].

Overall, these theoretical elements, structures, and properties of the materials highlight the potential of polymers, including hydrophobic and synthetic polycations, ionic polymers, and Lbl films, in mitigating bacterial and viral infections. Further studies along with exploration in this area can allow for the growth of effective biocidal and virucidal systems in combating infectious diseases.

5. CONJUGATED POLYELECTROLYTES (CPES) AND OLIGOMERIC PHENYLENE ETHYNYLENES (OPES) AS AN ANTIVIRAL AND ANTIMICROBIAL AGENT

5.1 Antimicrobial and Antiviral Mechanism of CPEs and OPEs

Conjugated polyelectrolytes (CPEs) are fluorescent polymeric materials having a π-conjugated backbone as well as pendant ionic functionalities. The backbone consists of delocalized electrons and is responsible for the optical, electronic, and semiconducting properties of CPEs [56]. CPEs have good photophysical properties. Pathogens can be detected and killed using CPE [57].

CPEs and OPEs can dissolve in water and have a high affinity for bacteria due to the existence of positively charged ionic side or end groups [58]. In aqueous solutions, CPEs rapidly aggregate by stacking the π-conjugated backbone through intra or interchain stacking. Consequently, there is a dramatic decrease in the fluorescence emission intensity [59]. Compared to CPE, OPEs can hold planar or near-planar configurations even with the number of side or end chains increasing [60].

CPEs and OPEs employ toxicity with Gram-negative bacteria on morphological as well as structural distortion of the cell envelope along with cytoplasm, and other components of the cell. On the other hand, CPEs and OPEs bind and rupture the Gram-negative bacteria's cell walls to kill them [58]. CPEs with a high molecular weight, including Cationic PPETh, possess a high affinity towards the exterior membrane of bacteria as they are negatively charged. CPEs destabilize the membrane of the bacteria and/or the peptidoglycan layer, which eventually kills the bacteria [61]. Small OPEs exhibit antibacterial activity by collapsing the cytoplasm membrane and disrupting the transmembrane electrochemical gradient of the cell [61]. Dark activity by CPEs and OPEs is possible because of the attraction among cationic polymers and oppositely charged bacterial membranes [62]. When irradiated with light, CPEs and OPEs exposed to bacteria produce Reactive Oxygen Species (ROS), possibly 1O2. ROS can infiltrate the bacteria which eventually leads to severe cell damage, resulting in the bacteria's death [63]. The primary method of exterminating bacteria with small OPEs is to cause the cytoplasm membrane to break down and/or disturb the electrochemical gradient of the cellular transmembrane [61]. In the dark, CPEs and OPEs partially disassemble the virus phage particle structure, which causes the virus to inactivate. Under UV/light irradiation, the phage capsid protein of the virus undergoes photochemical damage when both CPEs and OPEs are present [64].

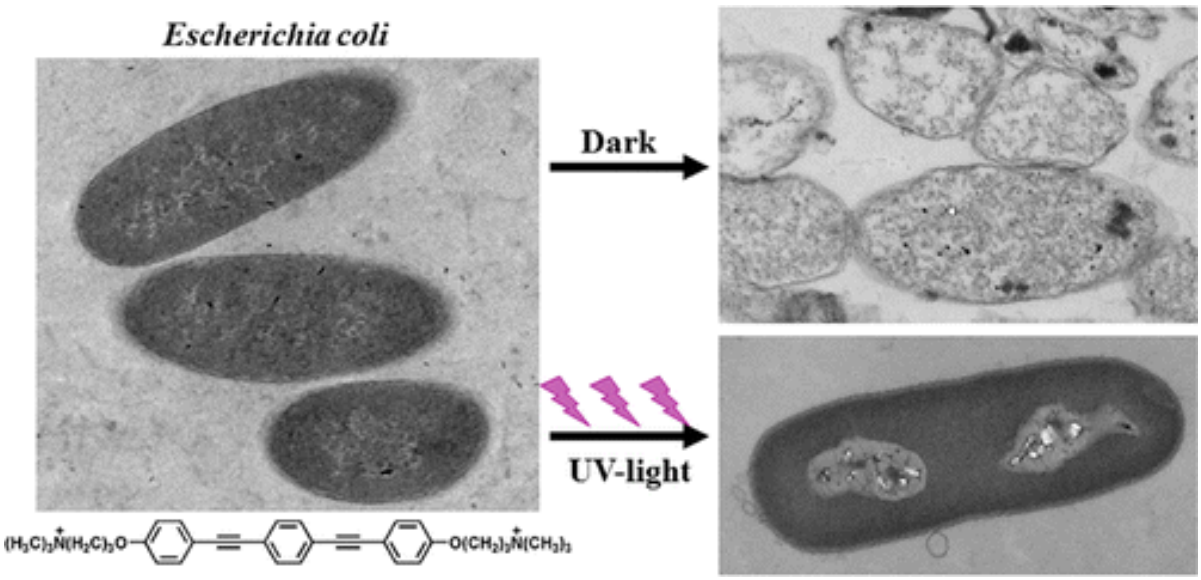

Figure 5. The structure of E. Coli bacteria following the exposure of CPE in Dark and UV light irradiation [58]

5.2 Antimicrobial Activity of CPEs and OPEs

Under light irradiation and in the dark, CPEs and OPEs have biocidal activity for both Gram-positive and Gram-negative bacteria. However, the biocidal activity is significantly reduced in the dark [65]. Almost all CPEs and OPEs exhibit noteworthy antiviral activity under UV/light irradiation, and most compounds also exhibit significant antiviral activity against viruses in the dark [64].

Water-soluble narrow band-gap CPE with a cationic Quaternary Ammonium (QA) substituent showed high affinity for *E. Coli*, with the binding between bacteria and CPE increasing with increased concentration. *E. Coli* gradually transforms from a negative to a positive surface with an increased concentration of CPE with QA side chains [66]. A new conjugated polymer (PFPhim), a cationic polymer with an Imidazolium backbone, exhibits potent antibacterial activity against E. Coli. The increasing

concentration of PFPhim from null to 16 μM reduces the Colony Forming Unit (CFU) of E. Coli bacteria to 94.7% [67]. A CPE with a phenyl ring is substituted by a thiophene ring in the poly (phenylene ethynylene) (PPE) repeat unit and was tested against *P. aeruginosa*. Under UV/light irradiation, the samples showed lower biocidal action. However, the thiophene-based CPE showed remarkable biocidal activity [68]. CPEs prepared by Lbl technology and deposited on a 5 μm diameter MnCO3 template showed intense antimicrobial activity against *Cobetia marina (C. marina)* and *P. aeruginosa* under light irradiation. After being exposed to white light for an hour, approximately 95% of the bacteria were killed. For *C. marina*, the bacteria are entrapped by the colloids, and most are killed after 15 minutes of exposure to white light. However, for *P. aeruginosa,* entrapment is lower resulting in a lower exposure time required for efficient killing [69]. Significant activity was shown by PPE-DABCO against vegetative cells without irradiation, with a CFU reduction by 2 orders of magnitude within 60 minutes. OPEs, on the other hand, such as EO-OPE-1 (C3), EO-OPE-1 (DABCO), and OPE-3, reduced the CFU of vegetative cells by ten-fold.

For comparison, in the dark, EO-OPE-1 (Th, C2) and PPE-Th exhibited little inactivation. Under UV irradiation, all the OPEs and CPEs are capable of inactivating the vegetative cells. When irradiated under UVlight, the EO-OPE-1(Th, C2) oligomer was the most effective in exhibiting antimicrobial activity against immobile and germinated ascospores [70]. Amyloid fibrils are oxidized by OPEs with minimal off-target oxidation. Anionic OPEs sensitize the oxidation of Aβ40 fibrils, which leads to their disassembly into shorter aggregates [71]. WMG1 and WMG2 which are two conjugated oligoelectrolytes (COEs) were fabricated using electron-rich thiophene and electron-poor benzo[1,2-c:4,5-c'] bis [1,2,5] thiadiazol (BBT), which are efficient photothermal agents. WMG1 exhibits vigorous antimicrobial activity against *B. subtilis,* a Gram-positive bacterium, in the dark. Furthermore, a concentration of 50 μgmL-1 WMG1 can reduce CFU from 25% to 2.5% when exposed to irradiation of 808nm. However, WMG1 shows no toxicity to Gram-negative *E. Coli* bacteria under dark and light conditions [72]. A membrane-intercalating COE PTTP exhibited highly efficient antibacterial activity against Gram-negative *E. Coli* bacteria at low light irradiation of 0.6 Jcm^{-2}. PTTP with a concentration below 10 μm is incorporated into the bacteria within 5 minutes of exposure. An estimated 99.5 percent of the bacteria were killed with a PTTP concentration higher than 2 μM. However, no toxicity is exhibited by PTTP in the dark [73].

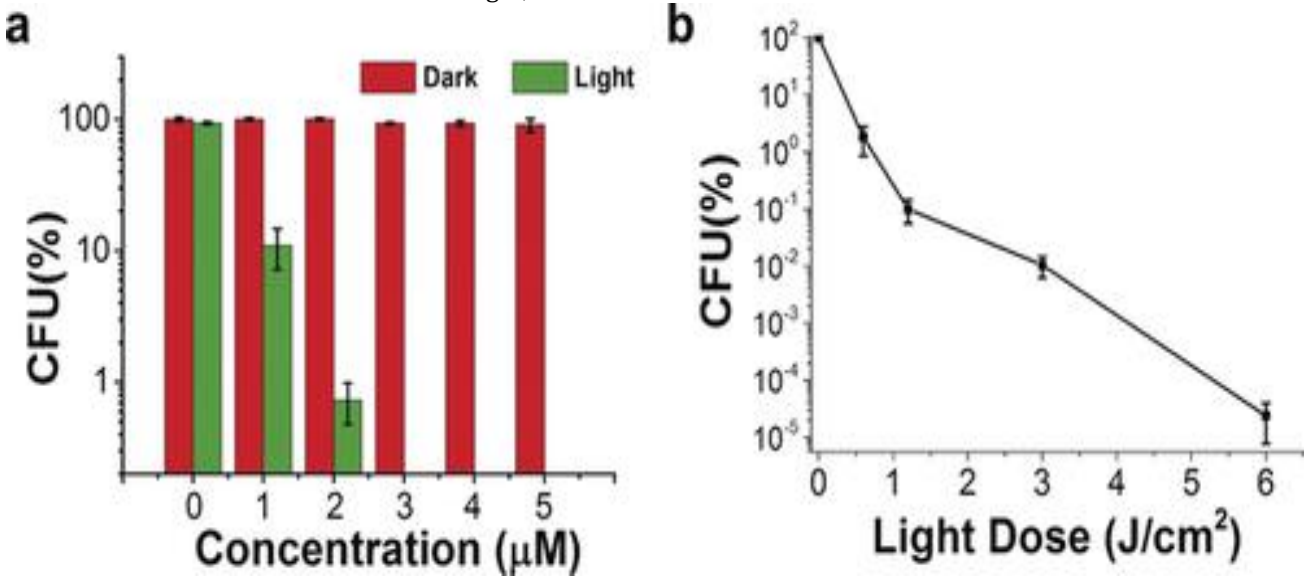

Figure 6 (a) – Dark and light-irradiated antimicrobial activity of PTTP against *E. Coli* bacteria vs concentration (5 min in 50 mM PBS) conducted by analysis of the colony forming units (CFU) on a Lysogeny Broth plate. A light dosage of 9 Jcm^{-2} was used (irradiation for 15 min at a fluence of 10 $mWcm^{-2}$). **(b) –** Antimicrobial activity of PTTP as a function of dose of light irradiation. *E. coli* was stained with 3 μM PTTP for 5 minutes before being exposed to light at a fluence of 10 mW cm^{-2} for various durations [73]

5.3 Antiviral Activity of CPEs and OPEs

Poly (Phenylene Ethynylene) based CPEs and OPEs were exposed to two viruses, T4 and MS2 bacteriophages. Under light -induced virucidal activity, all the polymers could inactivate both viruses, with PPE-DABCO showing the most significant antiviral activity. Although most polymers could efficiently inactivate the MS2 phage, most were only moderately effective against the T4 phage. PPE-DABCO and EO-OPE-1(Th) were the most effective in inactivating the T4 virus phage [64]. OPEs exposed to MS2 Viral Capsid strongly attach to the MS2 capsid protein assembly, and the binding energy can go up to -30 kcal/mol. In the grooves and indentions, OPEs bind along the exterior capsid protein surface; smaller OPEs exhibited the most robust binding. The study proves that OPEs are suitable antiviral agents against icosahedral-based viruses [74].

5.4 Cytotoxicity of CPEs and OPEs

Mammalian cells show toxicity with exposure to CPEs and OPEs. The CPE with QA substituent showed a higher affinity to bind with Gram-positive and Gram-negative bacteria than mammalian cells. Furthermore, upon light

irradiation of 808 nm, there was increased antimicrobial activity but no activity on mammalian cells [66]. A standard MTT assay carried out using a concentration of 16 μM of PFPhim, a cationic polymer with an imidazolium backbone, showed very weak toxicity to HeLa cells [67]. DABCO polymers and oligomers are cytotoxic to mammalian cells at low concentrations in the dark and only at the highest concentrations when irradiated with light. Thiophene-substituted polymers and oligomers are toxic to mammalian cells at moderate concentrations in the dark but can be cytotoxic at low concentrations in light - activated conditions. All the other CPEs and OPEs are only cytotoxic at high concentrations in the dark. [10]. Cytotoxicity to MCF-7 cells increases with the increase in polymer charge density and concentration of CPEs and decreases with increasing polymer aggregation. CPEs localized in lysosomes can infiltrate the mammalian cells. In the presence of mammalian cells, PIM4 and PIM2 can selectively bind to and deactivate the bacteria cells [11].

6. CARBON NANOMATERIALS (CNMs) AS AN ANTIVIRAL AND ANTIMICROBIAL AGENT

6.1 Antimicrobial and Antiviral Mechanism of Carbon-based Nanomaterials

Although the main mechanism of carbon-based nanomaterials (CBNs) is still being researched, it is believed to arise from the interaction between the nanomaterials and microbes. Three mainstream mechanisms are proposed for the antimicrobial activity, which includes nano-knives action from the sharp edges, oxidative stress, and wrapping of the bacterial membrane.
A single-walled carbon nanotube (SWNT) was exposed to *E. Coli* bacteria. Investigation of the mechanism was conducted by an in vitro study of single-walled carbon nanotube -mediated oxidation of glutathione, a redox state mediator in bacteria. The oxidation of glutathione was detected to rise when the fraction of metallic SWNTs was increased.

Scanning Electron Microscopy (SEM) images of nanotubes infested with E. Coli bacteria were shown to have morphological changes. Thus, a mechanism involving perturbation of the cellular membrane and bacterial oxidation followed by contact between SWNT and bacteria was proposed [75]. Furthermore, SEM images showed disruption of the bacterial cell membrane when graphene-based materials were exposed to *E. coli*. The graphene-based materials were also able to oxidize glutathione, suggesting oxidative stress as an antibacterial mechanism. Thus, an antibacterial mechanism of membrane stress due to the sharp edges of nanosheets as well as superoxide anion-independent oxidation was proposed [76]. In research conducted by Chen et al., Graphene Oxide (GO) was exposed to bacterial and fungal pathogens. SEM images showed an intertwining between the GO sheets and pathogens, which formed an aggregate and damaged the integrity of the cell membrane [77].

Carbon-based nanomaterials (CBNs) can exploit multiple methods for virus inactivation. The nanomaterials can distort the virus envelope or capsid organization. CBNs may also physically occupy the catalytic sites of the viral enzymes, which will exert a steric hindrance effect on the virus [12]. TEM images taken when GO was exposed to viruses show the destruction of glycoprotein spikes in the virion envelope. GO inactivates the virus before entry. Inactivation occurs due to the physical disruption of viral structure, which occurs as a result of the contact between the virus surface and the sharp edges of GO nanomaterials [78]. Replication of PRV and the porcine reproductive and respiratory syndrome virus (PRRSV) is suppressed when cells are treated with carbon dots (CDs) by initiating the interferon response [79]. The surface protein of viruses is destroyed by GO nanomaterials, followed by virus capture [80].

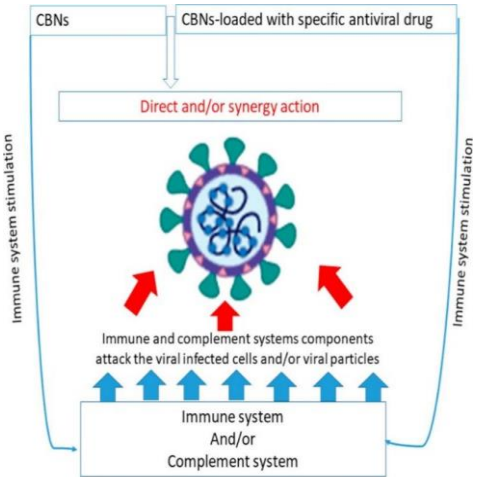

Figure 7. Proposed antiviral mechanism of CBNs. CBNs can work against viruses in three mechanisms: (1) Carbon-based Nanomaterials unaided; (2) aided by antiviral drugs; (3) aided by the components of the immune system[12]

6.2 Antimicrobial Activity of Carbon-based Nanomaterials

Carbon Nanomaterials exhibit potent antimicrobial activity. Nanomaterials (NMs) size plays a significant effect in their antimicrobial activity. Fullerenes, single-walled carbon nanotubes (SWCNTs), and Graphene Oxide (GO) nanoparticles and their derivatives are reported to be the most efficient antimicrobial agents [81]. The biocidal activity of these nanomaterials is influenced by the composition, modification of surface, and reaction environment, as well as the microorganism targeted [82].

E. coli bacteria incubated with SWNTs showed that the bacteria underwent membrane damage. The loss of cell viability of the bacteria shows that SWNTs exhibit potent antibacterial activity against the bacteria [83]. Multiwalled carbon nanotubes (MWNTs) and SWNTs treated with *E. Coli* showed strong levels of stress-related gene substances produced by the bacteria.

However, the quantity of gene products produced increased significantly in the presence of SWNTs compared to that of MWNTs [84]. The antibacterial activity of a nanocomposite of SWNT and electroactive polymer was investigated against *E. Coli* and *B Subtilis*. At a concentration of 1mg/mL, high inactivation of bacteria, 94% for *E. Coli* and 90% for *B. Subtilis* was accomplished [85]. Cationic Fullerenes with pyrrolidinium groups incubated with bacteria or fungal cells under white light elimination can kill more than 99.99% of the cells [86]. Fullerenes evaluated against E. Coli and B. subtilis were capable of inhibiting the bacteria at low concentrations of 0.5 – 1 mg/L for E. Coli and 1.5 – 3.0 mg/L for B. Subtilis. The biocidal activity was stronger for E. Coli bacteria. With high salt content media, aggregation of the fullerene particles occurs which reduces the antibacterial properties of fullerene [87]. GO at a concentration of 500 µg/mL was able to kill 90% of *P. syringae* and *X. campestris pv. Undulosa* bacteria [77].

6.3 Antiviral Activity of Carbon-based Nanomaterials

Carbon-based nanomaterials (CNMs) exhibited powerful virucidal activity towards several different viruses, such as positive-sense single-stranded RNA viruses. A polycarboxylic derivate of fullerene showed significant in vitro activity against influenza A virus and human immunodeficiency virus (HIV) [88]. Fullerene nanoballs at low nanomolecular concentrations showed antiviral activity against dengue and Zika virus. Fullerene nanoballs with greater (360) mannobiosides showed increased inhibitory activity against the two viruses [89]. Carbon Quantum Dots (CQDs) growing from hydrothermal carbonization of citric acid exposed to human coronavirus (HCoV) showed virus inactivation that was dependent on the concentration, with an approximate EC_{50} or 52 ± 8 µg/mL. CQDs that were obtained from 4-aminophenylboronic acid also distinguished virus inactivation with an EC_{50} or 5.2 ± 0.7 µg/mL [90]. Non-derivatized buckminsterfullerene was able to hinder the replication of simian immunodeficiency virus (SIV) in vitro as well as the activity of Moloney murine leukemia virus (M-MuLV) of reverse transcriptase (RT) (IC_{50} ≈3 µM) [91]. A high fraction of Japanese Encephalitis Virus (JEV) exposed to benzoxazine monomer-derived carbon dots (BZM-CDs) lost infectivity in the first 10 minutes of incubation, and no plague was observed at 5060 minutes of treatment. BZM-CDs caused a significant reduction in the infectivity of Zika Virus (ZKV) and Dengue Virus (DENV) to infect the cultured Vero cells [92]. Hydrophilic and dispersible carboxylated MWCNT (ox-MWCNTs) showed good antiviral activity against HIV with IC_{50} of 11.3 µg/mL and EC_{50} of 9.04 µg/mL [93]. Graphing quantum dots synthesized from multiwalled carbon nanotubes should have an anti-HIV activity with an IC_{50} value of 0.09 µg/mL and an EC_{50} value of 0.066 µg/mL [94].

6.4 Cytotoxicity of Carbon-based Nanomaterials

Carbon-based nanomaterials show low to no toxicity to human cells, especially at low concentrations. In vitro studies conducted with carbon dots on the human kidney, the embryonic 293T cell line showed no significant reduction of cell viability, even at a high concentration of 0.5 mg/mL. No obvious toxicity was also observed when mice were treated with CDs. [95]. Cell viability and morphology were not compromised in exposure scenarios of the human lung TCCC model to graphene oxide and graphene nanoplatelets [96]. No significant cytotoxicity was identified when short -chained (<10) functionalized graphene sheets were investigated against kidney Vero E6 cells, lung bronchial epithelial cells, and lung epithelial cells. Longer aliphatic chain graphene nanosheets with a concentration of 50 µg/mL reduced the cell viability significantly [97]. The cytotoxicity of Graphene Oxide is greatly reduced with a 10% concentration of FBS [98]. GO coated with a protein is considerably less cytotoxic to human cells [99].

6.5 Biocompatibility and Biodegradability of Carbon-based Nanomaterials

nanomaterials are primarily made of carbon, which is among the most fundamental substances in the human body. Due to carbon being the major element in these nanomaterials, it can promote tissue regeneration and is both biodegradable and biocompatible. In vitro study of Graphene Nanoplatelets (GNPs) showed GNP-C, which had a smaller size, to be more biocompatible than GNP-M. However, GNP-C was toxic at a higher concentration of 50 µg/mL. Complete oxidation of GNP-M shows that GNP-M is more bio -compatible until a concentration of 100 µg/mL [100]. Human myeloperoxidase (hMPO) and recombinant hMPO secreted by neutrophils can degrade graphene. The degradability behavior differs according to the physiochemical properties of the compound [101]. Degradation of the graphene oxide strongly depends on the hydrophilic nature of GO and its colloidal stability in the aqueous medium [102]. Degraded graphene oxide tested against a human bronchial epithelial cell line exhibited no toxicity or DNA damage to the cell. Thus, the degraded materials exhibit no genotoxicity to mammalian cells [103].

7. ANTIVIRAL COATING FOR THE INACTIVATION OF SARS-COV-2

The urgent need has been brought to light by the COVID-19 pandemic caused by the SARS-CoV-2 virus for strong preventative measures. The discovery of surface pollution as a key vector for viral transmission has boosted interest in creating antiviral coatings. Copper, polymers, and carbon-based nanomaterials are only a few of the materials whose potential has been investigated for the creation of antiviral coatings intended to render SARS-CoV-2 inactive. Table 2 summarizes the advantages and disadvantages of the material types.

Table 2. Advantages and disadvantages of the material types for antiviral coating

Method	Advantages	Disadvantages
Copper	Fast effectiveness, low cytotoxicity to humans, effective on dry and wet surface	Harmful to mammalian cells and aquatic, microbial resistance risk
Polymers	Effective in wet condition	Mechanically robust
CPEs and OPEs	High effectiveness in light condition	Effective only under UV irradiation, cytotoxic towards mammalian cells
Carbon-based Nanomaterials	High effectiveness and efficiency, not toxic to human cells, biodegradable and biocompatible	Effectiveness depends on aliphatic chain length, cytotoxic to eukaryotic cells,

7.1 Copper and Polymer Surface Coating against SARS-CoV-2

The antiviral characteristics of copper and polymers make them viable agents to extinguish SARS-CoV-2 from surfaces. When SARS-CoV-2 was exposed to a copper surface, no virus was detected after 4 hours [15]. There is rapid inactivation of the SARS-CoV-2 virus when exposed to copper and copper alloys by RNA destruction and significant structural damage [104]. Pure copper metal and CO-NPs were implanted in a polypropylene matrix and exposed to *E. coli* bacteria. After an exposure of 4 hours, 95% of the bacteria are killed. Copper oxide nanoparticles, compared to pure copper, were more effective in the inactivation of bacteria [105]. A hydrophobic long-chained polycation N, N-dodecyl, methyl-poly-ethylenimine (N, N-dodecyl, methyl-PEI) was used to coat glass slides. When exposed to Influenza A virus of both human and avian origin, the polycationic coating was effectively able to kill 100% of the virus. The coating is effective against the drug-resistant virus as well. Thus, the coating is a potential antiviral agent against all flu viruses [106].

A surface coating consisting of Cuprous Oxide (Cu_2O) particles adhered to polyurethane (PU) could inactivate the SARS-CoV-2 virus by 99.99% in 1 hour. The Cu_2O/PU coating can reduce the virus titer by 99.99% in glass and stainless steel after 1 hour. The wettability of the film affects the virus inactivation time. The film remained potent after five disinfection cycles and mechanically robust after being scratched by razor blades [7].

7.2 CPEs and OPEs against SARS-CoV-2

The antiviral and antimicrobial attributes of CPEs and OPEs can make polymers suitable agents against SARS-CoV-2. CPEs and OPEs exposed to SARS-CoV-2 showed effective antiviral activity under UV irradiation. In addition, one of the CPEs tested against SARS-CoV-2 exhibited antiviral activity at near-UV and visible light irradiation of 300 to 400 nm. However, in the dark, none of the polymers exhibited antiviral activity against the SARS-CoV-2 virus [9].

7.3 Carbon-based Nanomaterials (CNMs) against SARS-CoV-2

The Antiviral activity of CNMs against single-stranded positive-sense RNA viruses such as HCV, HCoV, HIV, and ZIKV has been demonstrated in various research. Since SARS-CoV-2 is also a single-stranded positive-sense RNA virus, carbon nanomaterials can be a potential agent for the inactivation of this virus. Graphene platforms with aliphatic chains of less than 10 carbon atoms showed moderate inhibition activity against SARS-CoV-2. With aliphatic chains of more than 9 carbon atoms, graphene sheets showed strong inhibition activity and could disrupt the coronavirus. Long aliphatic chain graphene platforms are capable of penetrating the cellular membrane to cause cell rupture and death. However, shorter chained platforms were not able to penetrate the cell membrane. Thus, long -chain compounds are needed for virus inhibition. Longer-chained graphene platforms were found to be highly cytotoxic to eukaryotic cells [97].

8.0 CONCLUSION

The review presents an overview of the recent information on the use of copper, copper compounds, polymers, and carbon nanotubes in mitigating the SARS-CoV-2 virus. Copper and its compounds have been proven effective as antimicrobial and antiviral agents, with copper oxide devices considered safe for skin contact. However, the potential for microorganisms to develop resistance to develop resistance to copper and its toxicity to mammalian cells raises concerns. Polymers like CPEs and OPEs exhibit strong antimicrobial and antiviral activity, particularly in light conditions, while some can also work in the dark. Copper and polymer coatings show promise in inactivating the SARS-CoV-2 virus, although research is needed to address the possibility of copper resistance. Graphene sheets have demonstrated the potential to occupy SARS-

CoV-2, but longer -chained materials show stronger antiviral activity at the cost of increased cytotoxicity. Further research on different carbon nanomaterials is necessary to determine their effectiveness in virus inactivation. Such research could also lead to shorter eradication times for viruses and bacteria in the future. to further advance the field, several potential future directions can be explored. Firstly, efforts can be focused on developing strategies to overcome or prevent copper resistance, as microorganisms have demonstrated the ability to develop resistance against copper. Understanding the mechanisms of resistance and finding ways to enhance the effectiveness of copper and its compounds as antimicrobial agents would be valuable. Additionally, the safety and biocompatibility of copper-based coatings should be thoroughly investigated, particularly regarding their long-term effects and potential toxicity on different surfaces and materials. This knowledge would be crucial for ensuring their widespread use without adverse effects. By pursuing these future directions, researchers can advance our knowledge of the potential benefits and limitations of copper, polymers, and carbon nanomaterials in mitigating the SARS-CoV-2 virus. The information will benefit the formulation of more effective approaches for viral eradication and help combat infectious diseases in the future.

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