Antimicrobial Nanomaterials and Coatings: Current Mechanisms and Future Perspectives to Control the Spread of Viruses Including SARS-CoV-2

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ABSTRACT: The global COVID-19 pandemic has attracted considerable attention toward innovative methods and technologies for suppressing the spread of viruses. Transmission via contaminated surfaces has been recognized as an important route for spreading SARS-CoV-2. Although significant efforts have been made to develop antibacterial surface coatings, the literature remains scarce for a systematic study on broad-range antiviral coatings. Here, we aim to provide a comprehensive overview of the antiviral materials and coatings that could be implemented for suppressing the spread of SARS-CoV-2 via contaminated surfaces. We discuss the mechanism of operation and effectiveness of several types of inorganic and organic materials, in the bulk and nanomaterial form, and assess the possibility of implementing these as antiviral coatings. Toxicity and environmental concerns are also discussed for the presented approaches. Finally, we present future perspectives with regards to emerging antimicrobial technologies such as omniphobic surfaces and assess their potential in suppressing surface-mediated virus transfer. Although some of these emerging technologies have not yet been tested directly as antiviral coatings, they hold great potential for designing the next generation of antiviral surfaces.

KEYWORDS: antiviral surfaces, antimicrobial coatings, pathogen-repellent surfaces, nanocoatings, photoactive materials, engineered surfaces, COVID-19, virus inactivation, virus repellent

The COVID-19 pandemic has intensified the world’s attention toward the spread of contamination facilitated by high touch surfaces. In response, surfaces and coatings capable of minimizing the presence of active viral pathogens are being explored for application in a variety of settings such as healthcare centers, long-term care facilities, public transport, schools, and various businesses to reduce human exposure and mitigate the spread of infectious pathogens.

One area of particular significance in the transmission of infectious diseases is the ability of microbes to survive on surfaces, both in healthcare settings and on common surfaces. Considerable research has been conducted to investigate solutions that prevent bacterial transmission and biofilm formation by killing and/or reducing attachment of microbes.

These have been realized through surface-bound active antimicrobials and biocidal coatings1 or passive pathogen-repellent surfaces2 developed using nanomaterials, chemical modifications, and micro- and nanostructuring.2−5

Many of the previously reported antimicrobial coatings have focused on antibacterial capabilities; however, there has been much less focus on antiviral surfaces and coatings. Persistence of active viruses on surfaces varies dramatically based on the...
type of the surface and the virus. For example, the viability of coronaviruses on surfaces ranges from 2 h to 9 days. Lack of host cells, immediate inactivation of some viruses on surfaces (e.g., Rinderpest virus), and incapability of some viruses to spread outside the body (e.g., human immunodeficiency virus, HIV) have attracted less attention to the transmission of viruses via surfaces. However, infectious viruses such as SARS-CoV-2 that remain viable on surfaces pose a great risk for transmission via the surface route, highlighting the urgent need for effective solutions that prevent the survival of viruses on surfaces. In order to highlight antimicrobial research which has definitively demonstrated antiviral capabilities, throughout this review, we will use the term antiviral to refer to nanomaterials and coatings which have proven antiviral capabilities, whereas the term antimicrobial will be used as a more general term to characterize nanomaterials and coatings that demonstrate effectiveness against other microorganisms, such as bacteria but to date have no proven antiviral capability.

A challenge encountered in reviewing the antiviral surface literature is related to the wide range of viruses used in testing. It is common to find tests conducted using bacteriophages, influenza, or HIV; however, there is often no systematic study that allows for the precise understanding of virucidal behavior. Viruses have a multitude of architectures—enveloped or non-enveloped, RNA-based or DNA-based—and can be further classified as positive- or negative-sense or single- or double-stranded, respectively. This is only the high-level variation witnessed in viruses, which illustrates the clear need for more robust testing when claiming antiviral capabilities.

Despite these caveats related to the lack of standardized evaluation methods, this review aims to provide a comprehensive summary of the current state of research toward antiviral materials and surfaces (Figure 1), using antimicrobial research as a starting point, whereas other review papers regarding reducing the spread of COVID-19 have focused on therapeutics and tools that inactivate SARS-CoV-2. First, we present a comprehensive review of metal and inorganic materials, with a focus on nanomaterials, with antiviral properties, namely, copper, silver, zinc, and titanium dioxide. We then discuss polymeric and organic surface coatings such as polyelectrolytes and photosensitizer materials that inactivate viruses (Figure 1). The toxicity and environmental concerns considered for each of these approaches will also be discussed. We finally present and propose emerging technologies that have not yet been used for antiviral purposes but hold great promise and potential for the future engineering of antiviral surfaces as they have been tested for their antimicrobial properties.
METAL AND INORGANIC MATERIALS AS ANTIVIRAL AGENTS

Copper. Copper is perhaps the most widely recognized and well-characterized antimicrobial metal used to date.\textsuperscript{12} Use of copper in medicine, as an antiseptic and anti-inflammatory agent, dates back millennia.\textsuperscript{13} Through bacterial investigations, modern research has identified multiple antimicrobial mechanisms for copper such as (1) plasma membrane permeabilization, (2) membrane lipid peroxidation, (3) alteration of proteins, (4) inhibition of protein assembly and activity, or (5) denaturation of nucleic acids.\textsuperscript{14} Membrane disruption can occur due to the electrostatic forces exerted by copper ions on the outer plasma membrane of cells.\textsuperscript{15} Damage to proteins occurs via the displacement of essential metals from their native-binding sites on proteins or direct interactions with the proteins.\textsuperscript{16} Copper-binding sites on nucleic acids also enable protein denaturation.\textsuperscript{17} Additionally, cyclic redox reactions between Cu\textsuperscript{+} and Cu\textsuperscript{2+} are known to produce highly reactive hydroxyl radicals. Reactive oxygen species (ROS) are either responsible for or contribute to cell death by interaction with the cell membrane.\textsuperscript{18}

Whereas some hypotheses have been made into the virucidal action of copper, the majority of antimicrobial copper research is focused on its antibacterial properties.\textsuperscript{12} Research has demonstrated that copper targets the viral genome, particularly encoding genes that are essential for viral infectivity (Figure 2a).\textsuperscript{19} It has been demonstrated that the primary effectors of inactivation for viruses such as murine norovirus are Cu(II) and Cu(I).\textsuperscript{20} Additionally, many researchers have postulated that the same ROS mechanism found in antibacterial activity can act on the viral envelope or capsid.\textsuperscript{12} Notably, viruses are susceptible to the damage induced by copper as they do not possess the repair mechanisms found in bacteria or fungi.\textsuperscript{14}

Mechanisms that result in the immediate deactivation of microbes upon contact are commonly referred to as “contact killing.”\textsuperscript{21} Researchers have taken advantage of this functionality to create copper-based antiviral surfaces (Table 1). Inactivation of influenza A was demonstrated on planar copper to be significantly higher than that on stainless steel, leaving only 500 infectious virus particles after 6 h from the 2 \times 10^6 virus particles inoculated, whereas stainless steel retained 500,000 infectious virus particles after 24 h.\textsuperscript{22} Influenza A and Escherichia coli bacteriophage (Qβ) were also tested on solid-state
| material form         | name               | envelope | genetic material | virucidal activity | deactivation time | proposed applications                                                                 | ref  |
|-----------------------|--------------------|----------|------------------|-------------------|------------------|----------------------------------------------------------------------------------------|------|
| solid state           | influenza A        | enveloped| negative-sense ssRNA | $2 \times 10^6$ reduced to 500 infectious virus particles | 6 h              | replacement of steel fittings; copper surfaces in schools and healthcare facilities      | 22   |
| solid (coupons)       | bacteriophage Φ6   | enveloped| dsRNA            | 2-log decline     | 1 h              | noted copper usage in sanitary and medical contexts                                      | 24   |
| solid state (coupons) | monkeypox          | enveloped| dsDNA            | complete viral inactivation upon contact | 3 min            | positioned as useful in hospital trials                                                  | 21   |
| copper alloys         | murine norovirus   | non-enveloped | positive-sense ssRNA | dependent on alloy composition |                 | suggest use of copper alloys as dry surfaces in health care and community environments to prevent spread of pathogens, in combination with regular and efficient cleaning and decontamination regimes | 20   |
| copper/zinc alloy     | human coronavirus 229E | enveloped| positive-sense ssRNA | inactivation for dry fingertip method $10^3$ PFU in wet-droplet contamination $(20 \mu L$ per cm$^2$) inactivated | dry touch: complete inactivation; wet fomite: range from complete inactivation to a $2$--$6$-log reduction; dry fomite: 5 to 120 min wet fomite: within 2 h | incorporation of copper alloy surfaces along with effective cleaning regimens and good clinical practice | 25   |
| solid-state oxide (cuprous oxide) | influenza A | enveloped | negative-sense RNA | 3.7-log reduction after exposure to $2.1 \mu$mol on glass slide | 30 min         | tackle novel forms of the virus and potential resistance to drugs to reduce transmission; treatment of both public and living spaces to help limit or prevent future pandemics | 23   |
| solid-state oxide (cuprous oxide) | bacteriophage Qβ | non-enveloped | positive-sense ssRNA | 6-log reduction | 30 min         | demonstrated potential for public and private living environments to reduce the risk of infections from pathogens | 18   |
| copper oxide within filters | rhinovirus-2 | non-enveloped | positive-sense ssRNA | $2 \pm 1.7$-log reduction | 2 min         | represent an inexpensive way to quickly deactivate viruses in contaminated liquids | 27   |
| yellow fever virus    | enveloped          | positive-sense ssRNA | $1.1 \pm 0.5$-log reduction | 2 min              |                 |                                                                                        |      |
| influenza A           | enveloped          | negative-sense RNA | $1.77 \pm 0.87$-log reduction | 2 min              |                 |                                                                                        |      |
| measles virus         | enveloped          | negative-sense RNA | $\geq 3.67$-log reduction | 2 min              |                 |                                                                                        |      |
| respiratory syncytial | enveloped          | negative-sense RNA | $1.5 \pm 0.5$-log reduction | 2 min              |                 |                                                                                        |      |
| parainfluenza virus 3 | enveloped          | negative-sense RNA | $1.11 \pm 0.5$-log reduction | 2 min              |                 |                                                                                        |      |
| Punta Toro virus      | enveloped          | negative-sense RNA | $1.73 \pm 1.55$-log reduction | 2 min              |                 |                                                                                        |      |
| Pichinde virus        | enveloped          | negative-sense RNA | $1.7 \pm 1.47$-log reduction | 2 min              |                 |                                                                                        |      |
| HIV-1                 | enveloped          | positive-sense ssRNA | $4.6 \pm 0.6$-log reduction | 2 min              |                 |                                                                                        |      |
Table 1. continued

| Material Form | Name               | Envelope | Genetic Material | Virucidal Activity | Deactivation Time | Proposed Applications                                                                 |
|---------------|-------------------|----------|------------------|--------------------|-------------------|---------------------------------------------------------------------------------------|
| **Copper**    |                   |          |                  |                    |                   |                                                                                       |
|                | adenovirus        | non-enveloped | dsDNA            | 2.2 ± 0.36-log reduction | 2 min             |                                                                                       |
|                | cytomegalovirus   | enveloped | dsDNA            | 4.3 ± 0.26-log reduction | 2 min             |                                                                                       |
|                | vaccinia virus     | enveloped | dsDNA            | 0.47 ± 0.45-log reduction | 2 min             |                                                                                       |
|                | influenza A        | enveloped | negative-segment RNA | no infectious titers recovered from surface | 30 min             | reduction of contamination risk during use or removal of masks                         |
| **Copper-oxide impregnated face masks** |                   |          |                  |                    |                   |                                                                                       |
|                | copper oxide       | impregnated | face masks      |                    |                   |                                                                                       |
| **Ionic impregnation of latex and filters** |                   |          |                  |                    |                   |                                                                                       |
|                | HIV-1              | enveloped | positive-segment RNA | latex: dose-dependent with incubation on glove surface | latent: 20 min     | example of reduction of nosocomial infections in hospitals using copper in fabrics, paper, latex, etc. |
|                | West Nile virus    | enveloped | positive-segment RNA | 5-log reduction | 5-log reduction |                                                                                       |
| **Zeolite textiles, Cu^{2+}** |                   |          |                  |                    |                   |                                                                                       |
|                | HSN1 avian influenza | enveloped | negative-segment RNA | Ck/Yamaguchi/7/04: >5.0-log reduction | Ck/Yamaguchi/7/04: >5.0-log reduction |                                                                                       |
|                | HSN3 avian influenza | enveloped | negative-segment RNA | >5.0-log reduction for WHO/Hokkaido/1/08: | WHO/Hokkaido/1/08: 1 min |                                                                                       |
| **Nanoparticles within coating** |                   |          |                  |                    |                   |                                                                                       |
|                | influenza H1N1      | enveloped | negative-segment RNA | complete inactivation | 1 min             | authors propose that this antipathogen coating can provide an additional measure of protection against the spread of diseases in natural and manmade disasters and during outbreaks of disease in either human or animal populations |
|                | copper powder       | within spray | negative-segment RNA | 100% inhibition  | 10 min             | demonstration of spray coating that is effective as an antimicrobial, which can be used on surfaces within healthcare facilities |
| **Hybrid coating (ionic)** |                   |          |                  |                    |                   |                                                                                       |
|                | HIV-1              | enveloped | positive-segment RNA | 99.8% reduction | 20 min             | broad-spectrum antimicrobial surface coating would have great impact on the battle against hospital-acquired infections; potential to provide antimicrobial protection on surfaces and materials in hospital settings |
|                | dengue virus       | enveloped | positive-segment RNA | 1.1-log TCID_{50} reduction | 4 h               |                                                                                       |
|                | HSV                | enveloped | dsDNA            | complete inactivation | 4 h               |                                                                                       |
|                | coxsackie         | non-enveloped | positive-segment RNA | 0.2-log TCID_{50} reduction | 4 h               |                                                                                       |
| **Silver nitrate in solution** |                   |          |                  |                    |                   |                                                                                       |
|                | feline calcivirus  | non-enveloped | positive-segment RNA | 3-log reduction in recovery in 2.1 mg/L concentration | 75 days             | technology proposed here would allow for custom design of active, adaptive packaging and contact surfaces |
|                | murine norovirus   | non-enveloped | positive-segment RNA | 1-log reduction after 75 days with 2.1 mg/L concentration | 75 days             |                                                                                       |
| Material Form | Name | Envelope | Genetic Material | Virucidal Activity | Deactivation Time | Proposed Applications |
|---------------|------|----------|------------------|------------------|------------------|-----------------------|
| nanoparticle in solution or film | feline calicivirus | non-enveloped | positive-sense ssRNA | in solution: 4-log reduction in recovery of virus if concentration was higher than 10.5 mg/L; as film: 1.42-log reduction of feline calicivirus at 25 °C complete inactivation of feline calicivirus at 37 °C | in solution: maintained over 150 days; as film: overnight incubation | as film: overnight incubation |
| nanoparticle impregnation of nanofiber sheets | influenza A (A/PR/8/34 (H1N1)) | enveloped | negative-sense RNA | 2-log decrease at concentration of AgNPs at 8.5 μL/cm² | 1 h | chitin-nanofiber sheets with potential to act as wound dressings |
| nanoparticle within graphene oxide | infectious bursa virus | non-enveloped | dsRNA | 0.125 mg/mL led to complete inhibition of 9 × 10⁴ TCID₅₀/mL; 1 mg/mL against the infection of 9 × 10⁴ TCID₅₀/mL | 1 h | further application of GO and GO-Ag can be considered for personal protection equipment to decrease the transmission of viruses |
| nanoparticle within membrane | feline coronavirus | enveloped | positive-sense ssRNA | 0.1 mg/mL caused 24.8% inhibition for 9 × 10⁴ TCID₅₀/mL; | 1 h | use as air filters within all types of public facilities |
| nanoparticle within membrane | bacteriophage MS2 | non-enveloped | positive-sense ssRNA | (5 ± 0.2) × 10⁶ PFU/mL completely removed | flow rate not reported | membranes used for water treatment |
| nanoparticle within membrane | bacteriophage UZ1 | enveloped | negative-sense RNA | 3.4-log decrease in virus load | flux of 3.1 L m⁻² h⁻¹ | development of an innovative strategy for preventing outbreaks of waterborne diseases |
| nanoparticle within film | feline calicivirus | non-enveloped | positive-sense ssRNA | >6-log TCID₅₀/mL reduction after contact with films | 24 h | excellent potential for PLA-silver films for food contact applications as well as in active packaging technologies for food safety and quality |
| nanoparticle within filter | bacteriophage MS2 virus | non-enveloped | positive-sense ssRNA | density of 1.5 × 10⁹ particles/cm² completely removed | 15 min | use as air filters within all types of public facilities |
| solid state | murine norovirus | non-enveloped | ssRNA | 1-log reduction for pure zinc; demonstrates roughly 70% antiviral efficiency without the presence of dust | 2 h | suggests the incorporation of copper alloy surfaces to help prevent infection spread, such as within hospitals |
| zinc oxide filopodia-like structures | herpes simplex virus type 1 | enveloped | dsDNA | dose-dependent reduction of viral entry; incubation with 100 μg/mL ZnO-MNs led to below 20% entry inhibition | 90 min | suggests development of these micro-nanostructures as a topical agent for prevention of HSV-1 infection |
| ionic solution | human rhinovirus | non-enveloped | positive-sense ssRNA | 99% reduction in number plaques using zinc chloride after virus exposure | 1 h | investigation focused on the mechanism of action |
| material form       | name                                | envelope | genetic material | virucidal activity | deactivation time | proposed applications                                                                 | ref |
|---------------------|-------------------------------------|----------|------------------|--------------------|------------------|----------------------------------------------------------------------------------------|-----|
| colloidal nanoparticles | Newcastle disease virus            | enveloped | negative-sense ssRNA | qualitative; chick allantoises did not hemagglutinate after incubation with nanocolloids | 96 h | starting point for the development of antiviral drugs                                   | 64  |
| solid-state coating | influenza virus                     | enveloped | negative-sense ssRNA | 3.6-log reduction (UVA intensity 0.1 mW/cm²) | 4 h | integration into surfaces in high-risk environments to reduce the spread of infection, such as at hospitals and daycare centers | 65  |
| feline calicivirus  | non-enveloped                       | positive-sense ssRNA | 1.7-log reduction (UVA intensity 0.1 mW/cm²) | 8 h |                                                                                      |     |
| solid-state anatase coating | bacteriophage Qφ              | non-enveloped | positive-sense ssRNA | 4.5-log reduction (UVA intensity 0.1 mW/cm²) | 4 h | prevention of viral transmission in indoor and outdoor living spaces                   | 52  |
| bacteriophage T4    | non-enveloped                       | positive-sense ssRNA | 2-log reduction (UVA intensity 0.1 mW/cm²) | 4 h |                                                                                      |     |
| fluorinated nanoparticles | bacteriophage MS2          | non-enveloped | positive-sense ssRNA | 2.6-log reduction (UVA intensity 0.01 mW/cm²) | 60 min | prevention of viral transmission in indoor commercial spaces with fluorescent lighting | 60  |
| feline calicivirus  | non-enveloped                       | positive-sense ssRNA | 2.0-log reduction (UVA intensity 0.01 mW/cm²) | 60 min |                                                                                      |     |
| murine norovirus    | non-enveloped                       | positive-sense ssRNA | 2.6-log reduction (UVA intensity 0.01 mW/cm²) | 6 min |                                                                                      |     |
| Ag- and Cu-doped nanowire membranes | bacteriophage MS2     | non-enveloped | positive-sense ssRNA | 4.02-log reduction after filtration | 30 min | filtration and disinfection of drinking water                                           | 67  |
| Ag-doped solid-state coating | influenza A          | enveloped | negative-sense ssRNA | ≥4.17-log reduction (15 W UVA light from 35 cm) | 20 min | disinfection of publicly used surfaces and breakdown of organic pollutants              | 62  |
| enterovirus         | non-enveloped                       | positive-sense ssRNA | ≥4.17-log reduction (15 W UVA light from 35 cm) | 20 min |                                                                                      |     |
| modified gold nanoparticle in solution | virus-like particles (VLPs), replicates human norovirus, GL1 VLPs | replicates | RNA | complete inactivation of VLPs at a concentration of 0.37 μg/mL using 0.083 μM Au/CuS NPs | 1 h | proposed as an antiviral                                                               | 68  |
| multivalent gold nanoparticles with sulfate ligands | HIV                   | enveloped | positive-sense ssRNA | <20% infection rate of T-cells after incubation with sulfonated gold nanoparticles | 30 min | development of a multifunctional therapeutic anti-HIV system                              | 70  |
| gold nanoparticles with undecanesulfonic acid-containing ligands | HSV-1                 | enveloped | dsDNA | irreversible loss of infectivity (0 PFU) after preincubation of virus with gold NPs | 1 h | production of virucidal drugs to fight viral infections                                  | 71  |
| HSV-2               | enveloped                         | dsDNA | irreversible loss of infectivity (0 PFU) after preincubation of virus with gold NPs | 1 h |                                                                                      |     |
| human papillomavirus type 16 | non-enveloped | dsDNA | irreversible loss of infectivity (0 FFU) after preincubation of virus with gold NPs | 1 h |                                                                                      |     |
| Virus Material Form | Name | Envelope | Genetic Material | Virucidal Activity | Deactivation Time | Proposed Applications |
|---------------------|------|----------|-----------------|-------------------|------------------|----------------------|
| Other inorganic antiviral materials | | | | | | |
| RSV | enveloped | negative-sense ssRNA | irreversible loss of infectivity (0 PFU) | 1 h | after preincubation of virus with gold NPs | |
| Vesicular stomatitis virus pseudotyped lentivirus (LV-VSV-G) | enveloped | negative-sense ssRNA | irreversible loss of infectivity (0 transduction units) after preincubation of virus with gold NPs | 1 h | | |
| Adenovirus-5 | non-enveloped | dsDNA | no inhibition (virus is not HSPG-dependent) | 1 h | | |
| Ion doping of coating with transition metals (i.e., iron, magnesium, manganese) | influenza H1N1 | enveloped | negative-sense RNA | 99% eradication with a fluorescent lamp | 30 min | suggests use for inactivation of virus inside buildings with fluorescent light |
| Silica nanoparticle in coating | influenza A/PR/8/34 (H1N1) | enveloped | negative-sense RNA | complete inactivation after incubation of virus suspension on surface | 30 min | use as a microbicidal coating |
| Nonstoichiometric perovskite-type | influenza A | enveloped | negative-sense RNA | neutralized 76% of influenza A | 15 min | proposed as a sterilizing method to minimize transmission of virus via multiple routes, including aerosol and contaminated fluids |

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Review
copper compounds and compared to solid-state silver compounds, with efficient inactivation achieved using cuprous oxide in a solid state but not cupric oxide or silver sulphide solid states. This difference between cuprous oxide solid-state copper and cupric compounds was in line with work by Sunada *et al.* using bacteriophage Φ6, which revealed a 6-log reduction for cuprous oxide (Cu$_2$O) in 30 min but a less than 1-log reduction on cupric oxide (CuO) in the same duration. In tests on copper coupons, a copper-mediated inactivation was illustrated for a range of bacteriophages by Li and Denneh.

This study included a range of double-stranded DNA, single-stranded DNA, and single-stranded RNA bacteriophages, with lipid-containing bacteriophages demonstrating the most susceptibility to copper in solution, such as *Pseudomonas* bacteriophage (bacteriophage Φ6) showing a 2-log reduction in the first hour. Studies using copper have also demonstrated significant reduction to orthopoxviruses, with monkeypox virus and vaccinia virus being inactivated within 3 min of contact with copper surfaces. Warnes and Keevil have highlighted the effectiveness of copper alloys, with 60% or...
higher copper component, in completely inactivating dry touch murine norovirus as fast as 5 min and showing significant reductions to wet fomite infectivity, up to complete inactivation within 60 min. Of particular interest for the current COVID-19 pandemic, in 2015, Warnes et al. investigated the use of copper alloys for the inactivation of human coronavirus 229E and showed that complete inactivation of 10⁶ plaque-forming units (PFU) applied to a 1 cm² coupon occurred in less than 60 min on a range of alloys, with Cu/Zn brasses being very effective at 70% or higher copper concentrations.

Researchers have also investigated the incorporation of copper ions into other materials to invoke antiviral capabilities. The research in this area was pioneered by Karlstrom and Levine in 1991 when the inhibition of proteases, proteins essential for viral replication, from human immunodeficiency virus 1 (HIV-1) was investigated under the influence of copper and mercury ions, Cu²⁺ and Hg²⁺. This study demonstrated that oxygen was not required for the inactivation of the protease, and that approximately stoichiometric concentrations of copper and mercury ions caused rapid and irreversible inactivation. Whereas this research notes that a clear cation-binding site exists on aspartic proteases, tests have also shown that copper does not directly inactivate these proteases. Instead, it is postulated that copper acts on the substrates for proteases, though this has not been clearly demonstrated.

Copper ions and particles have also been used in antimicrobial and antiviral textiles, filters, and polymeric materials such as latex. Early examples of this include the work by Borkow and Gabby, which created latex gloves impregnated with copper for testing against HIV-1 and copper filters tested with both HIV-1 and West Nile virus (WNV).

Antiviral effectiveness of latex samples in this study was based on the amount of copper incorporated in a dose-dependent manner, whereas the filters demonstrated a roughly 5-log reduction for both HIV-1 and WNV. Filters constructed from a layer of nonwoven polypropylene fibers on top of nonwoven carbon fibers were doped with copper oxide and investigated in a study by Borkow et al. that demonstrated reduction in various viruses, starting at a maximum of 2-log reduction of rhinovirus-2, and decreasing reductions were seen with yellow fever, influenza A, measles, respiratory syncytial, parainfluenza 3, Penta Toro, pichinde, HIV-1, adenovirus type 1, and cytomegalovirus, with vaccinia virus demonstrating the lowest reduction of just 0.47-log (see Table 1). Interestingly, copper oxide was incorporated into face masks, which resulted in the elimination of the human influenza A virus within 30 min, compared to 4.67 ± 1.35-log₁₀ TCID₅₀ (median tissue culture infectious dose) recovered from control masks (Figure 3a) by aerosolized challenge with 5.66 ± 0.51-log₁₀ TCID₅₀ of the virus. It has also been demonstrated that, using a cotton textile on which zeolite A was chemically synthesized, the structural component Na⁺ can be replaced with Cu²⁺ ions to then allow the textile to inactivate both highly pathogenic H5N1 and less pathogenic H5N3 influenza viruses.

Copper nanoparticles (CuNPs) present great promise for use in antimicrobial and antiviral surfaces due to their smaller size and high surface to volume ratio. This facilitates interaction with microbes and allows broad-spectrum antimicrobial and antiviral activity. Li et al. used CuNPs as part of a layered system by combining the antimicrobial and antiviral properties of copper and chlorine dioxide (ClO₂). This work investigated the use of a polymeric micelle preparation, coated on glass, for the slow release of ClO₂ over a 15 day span. In order to increase the contact killing efficiency of this material, CuNPs were covalently clustered on the micelle surface. Testing of this coating demonstrated a broad spectrum of activity that killed a range of microbes including viruses (H1N1), bacteria, and spores. Transmission electron microscope (TEM) images demonstrated significant degradation in virus structure upon contact with this coating (Figure 3b). The complete inactivation of the influenza virus was demonstrated via plaque assay with this coating within 1 min.

Finally, work published by Champagne et al. has demonstrated different methods of applying copper powder on surfaces. Specifically, they tested spray coating methods with copper powder to convey antimicrobial and antiviral effects. They also discovered that using a cold-coating approach, coating at a velocity of 500–1000 m/s and a temperature of 150–400 °C, similar to many commercial approaches that exist to apply metal coatings, was most effective against influenza A, with 100% inhibition after just 10 min of exposure to a 100 µL aliquot of virus.

Silver. Silver is another antiviral material that deactivates viruses by interaction with the viral envelope and viral surface proteins, blocking of viral penetration into cells, blocking cellular pathways, interaction with the viral genome, and interaction with viral replication factors. A significant portion of antiviral research for silver remains in solution. Nevertheless, previous studies have specifically investigated the use of silver in the form of ions, nanoparticles, and hybrid coatings to develop antiviral surfaces (Table 1). Work by Lara et al. aimed at elucidating the mechanism of viral deactivation for silver using HIV-1, suggesting that silver nanoparticles (AgNPs) function as early stage antivirals that disrupt viral replication. They hypothesized these to inhibit viral entry by binding or fusion to cells, though AgNPs also demonstrated inhibition at later stages in viral replication for which the mechanism was not confirmed. It is also evident that silver interacts differently with different families of viruses. Unlike copper, solid-state silver compounds do not appear to have strong antiviral capabilities. In a comparative study conducted by Minoshima et al., it was found that whereas solid-state cuprous oxide effectively inactivated influenza A virus and bacteriophage Qβ, solid-state silver sulfide showed little antiviral activity. Silver as an antimicrobial and antiviral has an affinity toward sulfur and phosphate groups, which can disrupt the cell membrane due to the interaction with phospholipid tails and proteins containing cysteine or methionine. Additionally, Ag⁺ produces ROS within cells, leading to an antimicrobial and antiviral ability. In bacterial studies, AgNPs are thought to disrupt the mitochondrial respiratory chain, leading to the production of ROS. More specific to antiviral activities, AgNPs are thought to inhibit the entry of the virus to cells due to binding of envelope proteins, such as glycoprotein gp120, which prevent CD4-dependent virion binding, fusion, and infectivity.

The use of metal ions within coatings is a common approach found in literature. A study conducted by Hodek et al. investigated the use of silver, as well as copper and zinc, as part of a sol–gel hybrid coating. Antiviral tests used HIV-1, dengue virus, herpes simplex virus (HSV), influenza virus, and coxsackievirus to provide comprehensive analysis on enveloped and non-enveloped, as well as DNA- and RNA-based viruses. Results were most favorable with HIV-1, with one method of
coating showing a 99.8% reduction in virus titer.\textsuperscript{42} Log-scale reductions were significant for all types of viruses (Table 1), though this coating was less effective against influenza and coxsackievirus, which is thought to be due to the nature of each virus as negative-sense RNA-based or non-enveloped, respectively.\textsuperscript{42} Castro-Mayorga et al. demonstrated the effectiveness of both silver nitrate and AgNPs in reducing recovered titer levels of norovirus surrogates for up to 150 days.\textsuperscript{38} Using feline calicivirus (FCV) and murine norovirus (MNV), statistically significant reductions in surface recovery of both viruses were seen in the presence of the ions and AgNPs (see Table 1). Notably, AgNP activity as an antiviral increased or remained constant up to 150 days if the concentration was higher than 2.1 mg/L; however, silver nitrate was most effective over only the first 75 days, likely due to the reduction and aggregation of ions.\textsuperscript{38} Here, silver nitrate was more effective against FCV, whereas AgNPs maintained higher and more prolonged effectiveness against MNV. This study further tested a AgNP film, produced by electrospinning a coating of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV)/AgNP fiber mats, which were tested at both 25 and 37 °C.\textsuperscript{38} Reductions of 1.42- and 0.14-log were demonstrated for FCV and MNV, respectively, at 25 °C, which were not shown to be statistically significant compared to control PHBV films exposed to the virus.\textsuperscript{38} At 37 °C, the reduction of FCV was greater than 2.26-log, whereas the reduction in MNV was less successful, at only 0.86-log. It is here hypothesized that the release of silver ions from the immobilized AgNPs are responsible for the viral inactivation observed here; however, further testing and research is required to confirm this mechanism.\textsuperscript{38}  

Similar to the work of Castro-Mayorga et al., AgNPs are combined with many different materials to lend antiviral capabilities. For example, chitin–nanofiber sheets (CNFS) have been combined with AgNPs to form antimicrobial and antiviral biomaterials including a 2-log decrease in influenza A.\textsuperscript{43} Integration of AgNPs into sheets was also the approach taken by Chen et al., with their research on the antiviral activity of graphene oxide sheets with silver particles (GO-Ag).\textsuperscript{44} Using both an enveloped and non-enveloped virus, researchers found that inhibition of viruses depended on the concentration of GO-Ag.\textsuperscript{45} The minimum concentration of GO-Ag required to inhibit infectious bursa virus (IBDV) inoculated at 9 × 10^2 TCID_{50}/mL was 0.125 mg/mL, whereas a higher inoculation of the virus, 9 × 10^3 TCID_{50}/mL IBDV, required 1 mg/mL of GO-Ag for inhibition. For inoculation of 4.7 × 10^4 TCID_{50}/mL of feline coronavirus, 0.1 mg/mL concentration of GO-Ag caused 24.8% inhibition.\textsuperscript{46} For this study, silver doubled the capability of graphene oxide sheets against enveloped viruses, whereas it was the sole source of inhibition against the non-enveloped virus.  

Integration of nanoparticles into membranes and filters is another common theme throughout the literature. Similar to copper, AgNPs can be incorporated into textiles and membranes in order to confer antiviral capabilities. Zdrowd et al. investigated the use of AgNPs with polysulfone membranes, which exhibit promising antiviral properties, although a significant loss of silver from the membrane resulted in short-lived antibacterial and antiviral activity.\textsuperscript{45} Although the exact mechanism for antiviral capabilities was not confirmed, the possibility of change in membrane permeability, depth of filtration, electrostatic adsorption, or inactivation by Ag\(^+\) ions allowed for influent concentrations of up to (5 ± 0.2) × 10^5 PFU/mL to be completely removed, whereas membranes without silver retained 10^5 PFU/mL.\textsuperscript{35} Similarly, work by De Gusseme et al. produced biogenic silver, which is associated with the bacterial cell surface of Lactobacillus fermentum, immobilized onto polyvinylidene fluoride (PVDF) membranes.\textsuperscript{46} This work tested antiviral properties using bacteriophage UZ1 and based on the slow release of Ag\(^+\), at least a 3.4-log decrease in virus load was achieved. Integration of silver into poly(lactic acid) (PLA) films functions in the same manner as biogenic silver on PVDF, with the slow migration of silver from the film as demonstrated by Martinez-Abad et al. when tested against FCV.\textsuperscript{47} Similar to this approach with membranes, silver can be integrated into filters in order to trap airborne virus particles. In research conducted by Joe et al., AgNPs were coated onto a medium air filter, which showed increased filter efficacy over 15 min of testing, with a density of 1.5 × 10^9 particles/cm\(^2\), demonstrating roughly 70% antiviral efficiency without the presence of dust.\textsuperscript{48} Importantly, efficiency increased with silver density but decreased as dust buildup accumulated.  

Research to date has demonstrated that the size of AgNPs influences their effectiveness as antiviral agents, with 25 nm as their upper size limit.\textsuperscript{49} Interestingly, Rogers et al. discovered that larger AgNPs—at diameters of 25, 55, and 80 nm—increase the number of plaque-forming units compared to controls, promoting virus survival.\textsuperscript{50} A proposed explanation for this is that when the AgNPs are too large to establish a strong physical interaction with the glycoprotein present on viruses, they are unable to inhibit viral binding to cell surfaces, and instead, these nanoparticles may agglomerate, facilitating interaction of the virus with the host cells.\textsuperscript{50}  

**Zinc.** Zinc has also been demonstrated as an antiviral agent since the publication of a study in 1974 by Korant et al. demonstrating its effectiveness against the human rhinovirus (HRV).\textsuperscript{53} Their use of 0.1 mM zinc chloride provided a 99.99% reduction in the number of plaques formed for HRV. It was also demonstrated in this work that the most dramatic effect of zinc as an antiviral was in inhibiting proteolytic cleavage, thereby halting the synthesis of viral polypeptides.\textsuperscript{53} As with most metals, the mechanism for antiviral applications varies between viruses. Studies have shown mechanisms that interfere with viral replication, including free virus inactivation and inhibition of viral uncoating, viral genome transcription, and viral protein translation and polyprotein processing (Figure 2c).\textsuperscript{53} For example, the effects of zinc on HSV-1 and -2 have been studied for over 40 years, and research has suggested antiviral functionality in all aspects of the virus life cycle including polymerase function, protein production and processing, and free virus inactivation.\textsuperscript{54–56} It is worth noting that many viruses rely on a zinc-finger architecture for their replication by host cells, demonstrating the relevance of zinc as an antiviral agent. **Zinc-fingers** are protein motifs that contain one or more amino acid sequence that allows the coordination of one or more zinc ions.\textsuperscript{57} Williams et al. illustrated that subtle changes in the zinc-finger structure of the nucleocapsid protein in HIV-1 reduced the effectiveness of chaperone activity that destabilizes nucleic acids during the reverse transcription process of viral replication.\textsuperscript{57}  

For antiviral surface applications, zinc is typically combined with other metals, whether as part of an alloy\textsuperscript{79} or as an ion within a coating.\textsuperscript{42} Researchers have investigated the use of solid surfaces containing zinc combined with copper to create an antiviral alloy. Surfaces showed synergistic capabilities
between zinc and copper with up to 40% zinc showing some efficacy to inactivate murine norovirus and alloys containing up to 30% zinc completely inactivating $5 \times 10^5$ PFU/cm$^2$ within 2 h. Notably, this study found a 1-log reduction in the infectivity of MNV using pure zinc, which conveys its capability as an antiviral on its own.

Zinc oxide (ZnO) has also been used to create structures that act as viricidal agents. Mishra et al. generated zinc oxide micro-nanostructures (ZnO-MNss), which mimicked the naturally occurring filopodia-like structures observed on the surface of HSV-1. These structures are thought to compete with the virus to bind heparan sulfate on the cell surface and also efficiently trap virions outside cells due to partial negatively charged oxygen vacancies. Preincubation of ZnO-MNss with HSV-1 for 90 min significantly blocked viral entry. Monitoring the enzymatic activity of infected cells measured using optical density showed that at a ZnO-MNS concentration of 100 $\mu$g/mL, below 20% of HSV-1 entered the cell, which increased to just below 30% entry when the ZnO-MNS concentration is at 0.1 $\mu$g/mL, whereas the phosphate-buffered saline control showed roughly 70% HSV-1 entry into cells. This reduction of virus cell entry was increased by the use of ultraviolet (UV) light to create oxygen vacancies in the structure of ZnO-MNss.

Zinc ionophores, substances responsible for transporting zinc ions across lipid membranes, are another intriguing use of the metal for antiviral capabilities. In research conducted by Qiu et al., the use of pyrithione (PT), which is a zinc ionophore, proved effective in inhibiting HSV-1 and HSV-2 replication. Here, PT facilitated the inhibition of HSV late gene expression and the production of viral progeny, which is presumed to be due to its role in the transport of Zn$^{2+}$, as inactivation was dependent on ion presence.

**Titanium Dioxide (TiO$\text{2}$).** TiO$\text{2}$ has attracted much attention for its photocatalytic properties and its resultant applications to the inactivation of bacteria and viruses. The mechanism of pathogenic inactivation in TiO$\text{2}$ is related to light absorption, electron/hole generation, and the oxidation of organic material by ROS, such as superoxide anions and hydroxyl radicals, generated via valence band holes and conduction band electrons (Figure 2d). As with other compounds, research into the antimicrobial properties of TiO$\text{2}$ has largely focused on antibacterial applications, leaving studies into its virucidal activity relatively scarce.

Early studies investigated the mechanisms of TiO$\text{2}$ inactivation of microbes in solution. Akhtar et al. developed TiO$\text{2}$ colloidal nanoparticles by a sonochemical method and demonstrated antibacterial and antiviral activity. The authors note that Gram-negative bacteria were more resistant to TiO$\text{2}$, citing enzymatic and DNA damage as probable mechanisms alongside membrane disruption. They qualitatively demonstrated antiviral activity by inoculating chick allantoises with Newcastle disease virus (NDV) and a sample of nanocolloids (see Table 1). The presence of active virus was characterized by hemagglutination of the allantois; virucidal behavior was demonstrated at concentrations above 6.25 $\mu$g/mL.

Planar surface coatings of TiO$\text{2}$ have been effective antibacterial agents. Nakano et al. tested the antibacterial activity of TiO$\text{2}$-coated glass slides on a range of bacteria, finding that all tested strains were photocatalytically inactivated on TiO$\text{2}$-coated glass under UVA exposure. They also demonstrated that Gram-negative bacteria were significantly more resistant to TiO$\text{2}$ catalysis, further implicating the lipid membrane as a locus of ROS activity. Krumdieck et al. report growing a nanostructured, solid, composite surface coating of anatase and rutile formations of TiO$\text{2}$ with carbon on stainless steel by a scalable vapor deposition method. The co-deposition of amorphous carbon enhances the photocatalytic activity of the coating by broadening the range of excitation wavelengths. They reported sizable reductions of bacterial activity under UV and visible light irradiation and under totally dark conditions (Figure 3c). Several studies have identified alterations to cell membrane potential, increasing permeability to damaging agents, as a possible “dark” mechanism of TiO$\text{2}$ antimicrobial action. These techniques are likely to be effective in antiviral applications, particularly against enveloped viruses in which the outer lipid membrane is susceptible to the same disruption mechanisms as the bacterial plasma membrane.

With the antibacterial nature of TiO$\text{2}$ nanoparticles and coatings well-established, some recent studies have focused on the direct application of TiO$\text{2}$ compounds to the development of antimicrobial—and, in growing numbers, antiviral—surfaces for use in areas with high rates of infection, such as hospitals. Nakano et al. demonstrated virucidal photocatalytic activity in TiO$\text{2}$ coatings using the enveloped influenza virus and non-enveloped FCV. They report a 3.6-log reduction in influenza virus activity after 4 h of UVA exposure on the TiO$\text{2}$-coated glass and 1.7-log inactivation of FCV after 8 h. Inactivation of the viruses past the lower detection limit of their experiment occurred at 8 and 16 h for influenza virus and FCV, respectively. Similarly to the bacterial case, they ascribe this stark difference to the absence of a phospholipid bilayer in non-enveloped viruses like FCV. Ishiguro et al. demonstrated antiviral activity of TiO$\text{2}$, spin-coated on glass plates against bacteriophages Q$\text{β}$ and T4 upon exposure to 0.1, 0.01, and 0.001 mW/cm$^2$ intensity UVA light (351 nm) (Figure 3d). The lowest intensities they tested are representative of the typical UVA irradiation encountered indoors. At the lowest intensity, they showed 5-log and 2-log reductions in viral activity after 24 h of irradiation for bacteriophages Q$\text{β}$ and T4, respectively. More rapid inactivation was observed at 0.1 and 0.01 mW/cm$^2$ for both viral species. They also hypothesized that the probable target of ROS released by photocatalysis is the protein capsid of the bacteriophage after performing tests with bovine serum albumin in solution as a competitor, which resulted in lower bacteriophage activation. The results of Nakano et al. discussed above indicate that this surface coating may perform better against enveloped viruses, in which the outer lipid envelope would be more effectively targeted than a protein capsid.

The effect of modifications to TiO$\text{2}$ surface coatings with fluorine compounds to increase the efficiency of ROS production is also an active area of research. Park et al. investigated the virucidal activity of fluorinated TiO$\text{2}$ surface coatings on bacteriophage MS2, FCV, and MNV. Their goal was to adapt the high-energy photon requirements of normal TiO$\text{2}$ photocatalytic activity through fluorination, which would allow the phenomenon to occur with only the intensity of UVA irradiation encountered in a typical office with fluorescent lighting (3.5 $\mu$W/cm$^2$ of UVA at a wavelength of $\sim$365 nm). They suspended TiO$\text{2}$ nanoparticles in a PEG solution before spreading, drying, and calcifying the mixture onto glass slides, followed by immersion in a NaF solution to achieve fluorination. They obtained 90% inactivation of bacteriophage MS2 under 3.5 $\mu$W/cm$^2$ of UVA ($\sim$365 nm) intensity.
after 42 min on glass with an F-TiO₂ surface coating. In a realistic office setting, residual UVA exposure from fluorescent lighting is typically around 2.4 μW/cm². Infectivity of MS2 on their coating fell below detection levels after 12 h under these conditions, validating the potential for F-TiO₂ coatings to prevent viral transmission in indoor environments. In addition, creating coatings that combine TiO₂ with other metals demonstrates higher viral inactivation (e.g., bacteriophage MS2) compared to coatings that contain only TiO₂. As demonstrated by Rao et al., loading TiO₂ nanowire membranes with silver and copper increased the disinfection of drinking water in comparison to TiO₂ alone or in combination with just one metal. Testing with bacteriophage MS2 demonstrated a 4.02-log reduction for Cu−Ag−TiO₂ in the UV light irradiation condition compared to that with less than 3-log reduction for TiO₂ alone, a difference that was attributed directly to the coloading of Ag and Cu. Furthermore, Moongraksathum et al. demonstrated the antiviral capability of a silver-doped TiO₂ coating prepared using a sol–gel method and deposited on a glass substrate. They achieved photocatalytic activity under both UVA and visible light irradiation, demonstrated by the degradation of a methylene blue solution, and observed that a 1 wt % concentration of Ag in the TiO₂ sol–gel produced the most photoactive coatings. They tested the antiviral capability of their coating against influenza A and enterovirus and achieved a >99.99% (>4.17-log) reduction in viral activity after irradiation with a 15 W UVA lamp for 20 min. They also confirmed that the Ag-TiO₂ composite outperformed a simple TiO₂ coating in terms of percent antibacterial effectiveness by more than 6 times.

**Other Inorganic Antiviral Materials.** Although copper, silver, zinc, and TiO₂ are the most widely studied inorganic materials, other inorganic materials and nanoparticles (e.g., gold, magnesium, transition metals, silica, and perovskites) have also been investigated in the antiviral research literature (Table 1).
Gold nanoparticles (AuNPs) have historically been used for drug delivery alone or in combinations with other, more viricidal, metals such as copper.68 Different surface modifications, such as increased porosity or sulfate-ended ligands, as well as combination with other bioactive metals, such as copper or iron, have been used to achieve antiviral and, more often, antibacterial functionality.68−70 Brogie et al. investigated a gold/copper sulfide core/shell nanoparticle which was able to rapidly inactivate norovirus GI.1 (Norwalk) virus-like particles that replicate the activity of human norovirus in solution.68 This work provided evidence that capsid protein degradation and capsid damage appeared to be the mechanism associated with viral inactivation, showing a direct reliance on nanoparticle concentration as well as treatment time. Reports as far back as 2010 from Di Gianvincenzo et al. hold promise for the use of capped gold nanoparticles as functional units that could be applied to surfaces to convey antiviral capabilities.70 These AuNPs were coated with multiple copies of an amphiphilic sulfate-ended ligand that is able to bind to HIV and inhibit the infection in vitro. More recent work by Cagno et al. seems to suggest a similar possibility for surface coating, this time implementing gold nanoparticles as well as iron oxide.71 Using long and flexible linkers that mimic heparan sulfate proteoglycans (HSPG), tests with HSV-2, vesicular stomatitis virus pseudotyped lentivirus (LS-VSV-G), human papillomavirus, and respiratory syncytial virus (RSV) illustrated the effectiveness as an antiviral agent.71

Use of transition metals, including iron, magnesium, and manganese, has also proven effective in combination with TiO2 due to their higher sensitivity to visible light for the creation of radicals. Choi and Cho created a visible-light-induced photocatalyst coating using a sol−gel method, which eradicated more than 99% of influenza virus H1N1 within 30 min.72 Here, the proposed mechanism of action is through the hydroxyl radicals that are generated in photocatalytic reactions, similar to the mechanisms discussed for TiO2 itself.72

A silica-nanoparticle-based antimicrobial and antiviral coating was developed by Botequim et al. by incorporating quaternary ammonium cationic surfactant, didodecyldimethylammonium bromide (DDAB), on the surface of nanoparticles.73 They showed complete inactivation of influenza A/PR/8/34 (H1N1) virus on glass coated with DDAB-treated nanoparticles with 0% virus survival. Notably, the antiviral mechanism does not require leaching of DDAB from the particle’s surface and is predicted to be similar to polycations with quaternary ammonium monomeric unity where they attract the viruses through favorable surface charges.73

Use of perovskites for antimicrobial capability is another growing area of research. Perovskites, referring to all compounds with the same crystal structure as calcium titanate, have been the subject of recent energy research, with perovskite-based solar cells reported in 2009.74 The application of these materials for antimicrobial and antiviral use has gained traction due to their superb oxidative ability, as reported by Weng et al.75 Using nonstoichiometric perovskite-type La0.5MnO3.9 research has demonstrated the oxidation of amino acid residues within the viral envelope which neutralized the infectivity of influenza A virus. The best disinfection was achieved using La0.9MnO3 drop-coated onto glass coverslips, which neutralized 76% of influenza A within 15 min.75 Additional research has remained focused on antibacterial capabilities of materials such as perovskite lanthanum aluminate (PLA) and La0.9Ag0.15MnO3 (LAMO) magnetic nanoparticles (MNPs), which are thought to function through the interaction of positively charged NPs with the negatively charged cell wall of bacteria such as Staphylococcus aureus, Bacillus subtilis, E. coli, and Pseudomonas aeruginosa.76−77

POLYMERIC AND ORGANIC ANTIVIRAL COATINGS

Polyelectrolyte-Coated Surfaces. It has been shown that the positive charge of polycations in polymers such as polyethylenimine attracts viruses having an inherent negative charge, interferes with their genomic content or structural units, and causes complete viral disintegration (Figure 4a).78,79 It has been claimed that this class of coating, typically applied through “painting”, can permanently convey antiviral and antibacterial properties even after being subjected to multiple washes.80 Herein, the literature involving polycations, mainly polyethylenimines, is discussed and is summarized in Table 2.

Immobilizing polycations on various surfaces has been shown to convey antiviral properties for both enveloped and non-enveloped viruses.81,82 Immobilized hydrophobic polyethylenimine-based and dendrimer-based polycations have reduced the titer of viruses. A study on bacteriophage PRD1 interaction with polyethylenimine-coated glass slides demonstrated that positive charges and hydrophobicity (conferred by 4-bromobutyrylated polyethylenimine-treated glass with N,N-dimethylhexadecylamine) result in a significant decrease in the virus titer compared to uncoated glass.82 Overall, having only polycations (minimal hydrophobicity) also showed a reduction in the virus titer; however, the combination of hydrophobicity with acetylated surfaces and positive charges of polyethylenimine was more effective.82 The antiviral activity was also proportional to the surface area of the treated glass. This was also confirmed by exposing treated glass powders to the virus solution, demonstrating a higher titer reduction compared to that on treated surfaces.82 Moreover, N-alkylated polyethylenimines, namely, linear N,N-dodecyl,methyl-polyethylenimines, have also demonstrated antiviral properties for non-enveloped viruses when “painted” on polyethylene.81 Using this method, Larson et al. showed slightly elevated antiviral activity as incubation time was increased and nearly 100% virucidal activity after 15 min of incubation.81 Furthermore, they tested another N-alkylated polyethylenimine, branched N,N-hexyl,methyl, via covalent attachment to glass slides and similarly demonstrated complete elimination of the rotavirus after 30 min of incubation.81 Their studies showed effective antiviral behavior of the polycation coating not only on enveloped viruses such as influenza but also on non-enveloped viruses such as poliovirus and rotavirus.81 To elucidate the role of the polyethylenimines, Haldar et al. demonstrated that their molecular weight is important for the virucidal characteristics, as they must be large enough to penetrate the viruses.83 They tested 750, 25, and 2 kDa sizes of polyethylenimines, with only the 750 kDa polyethylenimine showing complete inactivation of the influenza virus. Moreover, the polycation (polyethyleneimines) was compared to a polyanion and a neutral coating.83 It was shown that the polyanion has partial virucidal activity, whereas the neutral coating was not virucidal. The fact that both polycations and polyanions showed antiviral characteristics was hypothesized to be due to availability of both positively and negatively charged domains on the virus (i.e., influenza virus), with the negatively charged domains being dominant, which explains the superiority of polycations in antiviral activity (polycation and polyanion having 100 and
| material                                                                 | coating                        | method                                   | backbone material          | virus                                                                 | envelope   | genetic material | virucidal activity | deactivation time | proposed applications                       | ref |
|---------------------------------------------------------------------------|--------------------------------|------------------------------------------|-----------------------------|----------------------------------------------------------------------|------------|------------------|---------------------|-------------------|-----------------------------------------------|-----|
| 4-bromobutyrylated N,N-dimethylhexadecylamine                             | covalent bonding              | glass, glass powder                      | bacteriophages PRD1         | non-enveloped dsDNA                                                   | 77 ± 3% titer reduction | 24 h              | removing viruses from water by adsorption       | 82  |
| N,N-hexyl,methyl-polyethylenimines (750 kDa)                             | covalent bonding              | glass                                     | poliovirus                  | non-enveloped positive-sense ssRNA                                   | 100% virucidal activity (PFU/mL) | 30 min | disinfect aqueous solutions                      | 81  |
| N,N-dodecyl,methyl-polyethyleneimines (217 kDa)                          | physical absorption (painting)| polyethylene                              | poliovirus                  | non-enveloped positive-sense ssRNA                                   | ~100% virucidal activity (PFU/mL) | 30 min | disinfect aqueous solutions                      | 81  |
|                                                                           | physical absorption (painting)| polyethylene                              | rotavirus                   | non-enveloped dsRNA                                                   | 100% virucidal activity (PFU/mL) | 15 and 30 min | disinfect aqueous solutions                      | 81  |
|                                                                           | physical absorption (painting)| glass, polypropylene, polyethylene       | influenza strain WSN/33 (H1N1), PR/8/34 (H1N1), turkey/MN/833/80 (H4N2) | non-enveloped negative-sense dsRNA                                  | 100% virucidal activity (PFU/mL) | 5 min  | not specified                                       | 79  |
| N,N-hexyl,methyl-polyethylenimine (Mw nonspecified)                       | covalent aerosol-assisted plasma deposition | glass                                     | influenza A/PR/8/34 (H1N1)  | non-enveloped negative-sense dsRNA                                   | >4-log reduction in viral titer | 10 min | not specified                                       | 89  |
| N,N-dodecyl,methyl-polyethyleneimines (750 kDa)                          | physical absorption (painting)| glass                                     | influenza virus A/WSN/33 (H1N1) | enveloped negative-sense ssRNA                                       | 100% virucidal activity (PFU/mL) | 30 min | preventing the spread of influenza               | 83  |
|                                                                           | physical absorption (painting)| glass                                     | influenza A Wuhan (H3N2), avian influenza A turkey (H4N2) virus, drug-resistant strains of a human influenza A Wuhan (H3N2), and an avian influenza A turkey (H4N2) | enveloped negative-sense ssRNA | final viral titer (PFU/mL) = 0 | 30 min | preventing the spread of influenza               | 87  |
| N,N-dodecyl,methyl-polyurethane (Quat-12-PU)                             | solution treated or nanoparticle treated by spray coating (physical absorption) | glass                                     | influenza virus             | enveloped negative-sense ssRNA                                       | final viral titer (PFU/mL) = 0 | 15 min | not specified                                       | 88  |
| polyethylenimine (25 kDa)                                                 | chemical cross-linking (covalent) | glass, microfiltration membranes          | bacteriophage MS2            | non-enveloped positive-sense ssRNA                                   | 4-log of reduction in the virus titer | 30 min | filtration membranes for drinking water          | 78  |
| coating                          | method                        | backbone material | name                  | envelope   | genetic material | viralcidal activity          | deactivation time | proposed applications                              | ref |
|---------------------------------|-------------------------------|-------------------|-----------------------|------------|-----------------|-----------------------------|------------------|-----------------------------------------------------|-----|
| polyethyleneimine (25 kDa) + AgNP and/or CuNP | chemical cross-linking (covalent) | glass, microfiltration membranes | bacteriophage MS2 | non-enveloped | positive-sense ssRNA | 4.5- to 5-log reduction in the virus titer | 30 min | filtration membranes for drinking water | 78  |
| quaternary ammonium compounds (QACs) | physical absorption by thin layer deposition | glass, plastic | influenza A (H1N1) | enveloped | negative-sense ssRNA | complete inactivation | 1 h | not specified                                   | 90  |
| Polycations                     |                               |                   | poliovirus Sabin 1    | non-enveloped | positive-sense ssRNA | no inactivation observed | 1 h | antimicrobial surfaces                            |     |
| pol(vinyl alcohol-co-ethylene) nanofibers functionalized with benzophenone tetracarboxylic dianhydride and chlorogenic acid | electrospinning followed by grafting | N/A (standalone membrane) | bacteriophage T7 | non-enveloped | dsDNA | 5-log PFU/mL reduction | 5 min daylight exposure | protection of high-risk surfaces and personal protective equipment (e.g., protective suit) | 94  |
| Photosensitizer materials       |                               |                   | dengue-1             | enveloped | positive-sense ssRNA | final viral titer (PFU/mL) = 0 | 30 min illumination | integration in textiles for the prevention of nosocomial infections | 95  |
| free-base S-(4-aminophenyl)-10,15,20-tris(4-N-methylpyridinium)porphyrin (A^B_3^+) | covalent bonding | nanofibrillated cellulose | vesicular stomatitis virus (VSV) | enveloped | negative-sense ssRNA | final viral titer (PFU/mL) = 0 | 30 min illumination | integration in textiles for the prevention of nosocomial infections | 95  |
| metalted S-(4-aminophenyl)-10,15,20-tris(4-N-methylpyridinium)porphyrinatozinc(II) (Zn-A^B_3^+) | covalent bonding | nanofibrillated cellulose | vesicular stomatitis virus (VSV) | enveloped | negative-sense ssRNA | final viral titer (PFU/mL) = 0 | 30 min illumination | integration in textiles for the prevention of nosocomial infections | 95  |
| cationic porphyrin              | covalent bonding              | cellulose fiber (paper) | dengue-1             | enveloped | positive-sense ssRNA | >99.995% reduction in FFU/mL | 30 min illumination | autonomously sterile materials for hospitals and healthcare-related industries, preventing the spread of infection | 96  |
| rose bengal                     | covalent bonding              | wipes with polypropylene fibers | dengue-1             | enveloped | positive-sense ssRNA | ~99.9% reduction in FFU/mL | 30 min illumination | one-step procedure for cleaning and disinfecting influenza virus-contaminated surfaces | 97  |
| C\textsubscript{60}             | covalent bonding              | SiO\textsubscript{2} electrospayed on a stainless steel mesh | bacteriophage MS2    | non-enveloped | positive-sense ssRNA | 3 h illumination | remote disinfection |                                             | 98  |
66% viricidal activity, respectively. Similarly, a study by Dang et al. showed positively and negatively charged polyelectrolyte multilayers (PEMs) deposited on a quartz crystal microbalance. They claimed that with various designs for the PEMs it is possible to manipulate the adhesive properties of the surfaces toward viruses. Negatively charged surfaces (e.g., poly(styrene-4-sulfonate)-terminated) showed relatively lower amounts of bacteriophage MS2 due to the unfavorable electrostatic interaction between the bacteriophage and the anionic surface. On the other hand, positively charged PEMs showed higher amounts of MS2 deposition, which is in line with the findings by Haldar et al. From the molecular perspective, polycations with both branched and linear polyethylenimines (e.g., N,N-dodecylmethylpolyethylenimine) were lethal toward influenza virus A, even to strains which were resistant toward commercial drugs. PEMs can be easily applied to surfaces using methods such as spray coating, dip coating, and painting for the development of scalable antiviral coatings.

Further studies by Hsu et al. investigated the role of the underlying substrate on the antiviral properties. Polyethylene and polypropylene were used as alternatives to glass. It was discovered that all three types of substrates used for coating demonstrated complete disinfection of the virus, proving that the polycation painting is the key to the antiviral activity of the materials. In order to better understand the mechanism and fate of viruses when coming in contact with the polycation coating, the viral nucleoprotein was assayed using colorimetric ELISA as a marker indicating viral rupture. The assay demonstrated the disappearance of the viral particles from the solution exposed to the polycation, indicating that the viruses attach to the hydrophobic polycationic coatings (Figure 4a). Furthermore, real-time reverse-transcriptase PCR (qRT-PCR) was used to evaluate the detectable viral RNA in solution where its presence would indicate loss of infectivity of the virus due to the viral genomic material being exposed. It was shown that a significant amount of viral RNA was detectable; therefore, the polycation layer is not only attracting the virus but also inactivating the virus. This was also validated with scanning electron microscopy (SEM) (Figure 4b) of the influenza virus, showing that the integrity of the influenza virus was compromised for 54% of the 132 surveyed viruses.

Another class of polyelectrolytes used as antiviral coatings is polyurethane-based materials, such as N,N-dodecylmethylpolyurethane (Quat-12-PU), which are versatile, abrasion-resistant, and robust for long periods of time.
can be coated onto surfaces through three different methods: (1) spray coating on polyethylene or glass slides, (2) synthesizing Quat-12-PU nanoparticles by dissolving Quat-12-PU in tetrahydrofuran and subsequently spraying the nanoparticle solution on glass slides (SEM image shown in Figure 4c i and ii), or (3) by electrospinning Quat-12-PU nanofibers onto glass slides (scanning electron microscopy image shown in Figure 4d).88 The study by Park et al. demonstrated antiviral properties with complete inactivation of influenza virus (enveloped, with 0 PFU/mL of virus detected) but not poliovirus (non-enveloped) by subjecting the solution-treated or nanoparticle-treated surfaces to the respective virus solutions and comparing each to uncoated substrates (Figure 4e).88 The antiviral properties were attributed to the Quat-12-PU interfering with the lipid envelope of the virus protecting its RNA. Comparing the Quat-12-PU to the N,N-dodecyl-
methyl-polyethylenimine-coated surfaces, it was previously shown that the latter disinfects poliovirus. Park et al. showed that the polioviruses adhere to N,N-dodecyl,methyl-polyethylenimine surfaces but not to Quat-12-PU-coated ones by subjected N,N-dodecyl,methyl-polyethylenimine surfaces to detergent washes and assessing the extent of the recovered viruses. This can be attributed to the different chemistries on these surfaces. 

A polyelectrolyte-based method was used to develop filtration membranes for reducing the amount of virus in drinking water. Through a covalent layer-by-layer deposition method, multiple layers of polyethylenimine were created with use of terephthalaldehyde as the cross-linking agent. It was found that there was a 4-log reduction in the virus titer from the solution. Furthermore, silver and copper nanoparticles were incorporated within the polyethylenimine layer and tested for antiviral properties, indicating 4.5- to 5-log reduction in PFU. They also ran qRT-PCR on the permeates of the membranes, which confirmed the hypothesis that the polycationic coating actually inactivates the virus and exposes the genomic content. Their overall findings suggested that this polyelectrolyte coating can be integrated on a planar surface (e.g., glass), as well as on irregular surfaces (e.g., porous membranes).

In another study, quaternary ammonium compounds (QACs) were coated onto glass and plastic surfaces in order to add antiviral properties. The QAC polymer was dissolved in acetone, and a thin layer was added to either glass or well plates and subsequently dried, making a positively charged layer. Enveloped influenza A (H1N1) virus and non-enveloped poliovirus Sabin 1 were tested for virucidal activity on the surfaces. Influenza A showed reduction in the virus infectivity after 2 min; on the other hand, poliovirus did not show reduction even after longer incubation times.

**Photosensitizer Materials.** A number of recent studies have integrated photosensitive compounds other than TiO₂, such as rose bengal and C₆₀, onto surfaces to exploit the ROS-dependent antimicrobial and antiviral pathways. Photosensitizers, light-activated molecules, are also used for antimicrobial photodynamic therapy as an alternative for antibiotic chemotherapies.

Antimicrobial photodynamic inactivation operates on the principle that a photosensitizer gets excited via visible light absorption and subsequently reacts with oxygen. There are two pathways (type I and type II), shown in Figure 5a, through which active products are generated that induce damage to viruses, bacteria, or other organic species. In the type I pathway, the photosensitizer reacts with bio-organic molecules and produces ROS (e.g., superoxide, hydroxyl radicals, and hydrogen peroxide). The type II pathway occurs as the excited photosensitizer transfers energy to molecular oxygen and generates singlet oxygen (¹O₂), which induces oxidative damage to biological species. More specifically, saturated lipids are the target for free radicals and singlet oxygen attacks. This leads to lipid peroxidation and the alteration of surrounding proteins, nucleic acids (mainly guanine), and other molecules. Therefore, it is hypothesized that the generation of ROS damages the viral envelope and causes viral inactivation. This makes enveloped viruses more susceptible to photodynamic inactivation than non-enveloped ones. However, non-enveloped viruses have also shown photodynamic inactivation of their viral proteins. The advantages of such antimicrobial pathways over antiviral and antimicrobial drugs include nonspecific damage leading to an inability to develop resistance, ¹O₂ being environmentally benign, and the nontoxicity of photosensitizers.

Si et al. reported on developing a fine membrane of electropun poly(vinyl alcohol-co-ethylene) nanofibers functionalized with benzophenone tetracarboxylic dianhydride and chlorogenic acid. They recognized the limitations of UV-dependent photoactivity exhibited by most photoactive materials and sought to develop an antibacterial and antiviral surface excitable in daylight conditions by ambient visible and UVA light. They achieved a 5-log reduction in viral activity of bacteriophage T7 in daylight conditions, with similar results for antibacterial action against E. coli and L. innocua. As mentioned previously, non-enveloped bacteriophages such as T7 generally show increased resistance to most ROS- or contact-killing-based antiviral mechanisms, and the authors predicted that enveloped viruses would be targeted even more effectively due to the presence of a lipid membrane. The nanofiber membrane is also notable for its filtration capabilities, which effectively impedes the penetration of small particles and micro-organisms. It also possesses the ability to “store” photoactivity by achieving a metastable electronic structure in the event that hydrogen abstraction is not completely reversed by ROS production. This allows it to maintain its antimicrobial characteristics in the dark. Si et al. tested their nanofiber membrane on personal protective equipment such as lab coats and N100 masks and demonstrated that it provided a nearly 6-log reduction in T7 phage plaque-forming units compared to the unmodified materials.

Cellulose has been researched with the aim to reduce nosocomial infections in hospital textiles. In order to introduce antimicrobial and antiviral characteristics to cellulose, Alvarado et al. developed photosensitizer-linked nanofibrillated cellulose (PS-NFC) through utilizing triazine linking and covalently bonding a porphyrin-based photosensitizer to nanofibrillated cellulose (NFC).

The antiviral behavior of this technology relies on the production of reactive singlet oxygen (¹O₂), and other ROS upon illumination of the photosensitizer and the extremely high surface area of NFC is a contributing factor. Free-base [5-(4-aminophenyl)-10,15,20-tris(4-N-methylpyridinium)porphyrin (A³B³⁺⁺)] and metalated [5-(4-aminophenyl)-10,15,20-tris(4-N-methylpyridinium)-porphyrinato] zinc(II) (Zn-A³B³⁺⁺) photosensitizers were applied to NFC (A³B³⁺⁺-NFC and Zn-A³B³⁺⁺-NFC) (Figure 5b,c) in order to integrate photoactive behavior to NFC. Vesicular stomatitis virus (VSV) and dengue-1, both enveloped viruses, were used to assess the antiviral behavior of the modified NFC. After illumination, both treated NFC materials showed complete inactivation of the viruses (Figure 5d,e). A study by Carpenter et al. conjugated cationic, anionic, and neutral porphyrins to cellulose fibers to add antimicrobial properties to the surface against enveloped (dengue-1 and influenza A) and non-enveloped viruses (human adenovirus-5 (Had-5)). The anionic and neutral porphyrins did not show promising results in a reduction in colony-forming units (CFU)/mL in their bacteria studies, which they attributed to electrostatic repulsion and/or hydrophobicity of those surfaces not allowing interaction of the porphyrins with the bacteria. For the virus studies, they implemented porphyrin-positive treated cellulose, due to its better performance with bacteria. Dengue-1 and influenza A showed >99.995% and ~99.5% reduction in focus-forming units (FFU)/mL, however, the non-enveloped
viruses (HAD-5) were harder to inactivate and showed ~99% reduction in FFU/mL using immunofoci staining. The reductions in FFU were attributed to the protein-based capsid and the lipid bilayers, which in the case of enveloped viruses were found to be less resistant toward photosensitization.96 In another study, wipes with polypropylene fibers were coated with the photosensitizer rose bengal, which is immobilized on the fibers through multiple amide bonds and produces singlet oxygen during exposure to visible light.97 Wipes were spiked with various viruses including the human norovirus GI.4 and GI.4, murine norovirus 1 (MNV-1), human adenovirus type 5 (hAdV-5), and influenza virus H1N1. The non-enveloped viruses did not exhibit prompt inactivation, with the time needed for the first 1-log reduction being more than 7 h, whereas enveloped viruses showed immediate and complete inactivation (more than 4-log).97 Furthermore, the transfer and persistence of viruses from a steel surface were tested after being wiped with the treated and untreated wipes, and the proportion of viruses recovered from the wiped surface to the unwiped one through viral genome quantification was reported. For MNV-1 and influenza virus, no viruses were discovered after wiping the contaminated steel surfaces. However, residual amounts (0.2–0.6% residual virus proportions) of norovirus were found on the steel surfaces.97 Notably, in this case, no difference was found between the treated and untreated wipes. They further tested the already used wipes (used on steel surfaces) on a secondary steel surface to investigate cross-contamination and revealed that non-enveloped viruses demonstrated cross-contamination.97 The development of wipes that remain clean is an avenue for reducing cross-contamination and halting the spread of infection via surfaces.

A C_{60}-based sensitizer was developed to evaluate virus inactivation in air due to its high yield of singlet oxygen production. Briefly, SiO_{2} was electrospayed on a stainless-steel mesh to serve as a support for a layer of (3-aminopropyl)-triethoxysilane (APTES).98 This allowed for the SiO_{2} to attach to the double bonds of C_{60}. To assess antiviral activity in air, inactivation rates of bacteriophage MS2 were evaluated at various distances from the singlet oxygen source (C_{60}-coated mesh).98 The schematic of the production process and virus assay setup are shown in Figure 5f. It was found that bacteriophage MS2 was deactivated inactivation of (N_{0} − N)/N_{0} the quantity of the residual bacteriophage MS2 remaining relative to the initial quantity in PFU/mL) by 55.8, 37.7, and 24.3% when the C_{60}-coated mesh was used at 5, 15, and 30 cm distances, respectively, after 3 h.98

Within the field of photosensitized material and their virucidal activity, there are some studies that produce polycaprolactone, polyurethane, and polycrylonitrile nanofibers and dope them with photosensitizers such as 5,10,5,20-tetraphenylporphyrin, polycrylonitrile, and porphyrin positive charges and dope them with photosensitizers such as 5,10,5,20-tetraphenylporphyrin, polycrylonitrile, and porphyrin positive mixtures while electrospinning the fibers.99,100 These have been shown to inactivate non-enveloped viruses such as polymavirus (30 min, quantification was not elaborated) and adenovirus 5 (30 min, ~99.8% reduction in PFU/mL), as well as enveloped viruses such as baculoviruses and VSV.99,100

**Other Coatings.** To introduce antiviral properties to textiles, Iyigundogdu et al. immersed cotton fabrics into a solution containing sodium pentaborate pentahydrate and triclosan.101 They tested adenovirus type 5 and poliovirus type 1, demonstrating that the amount of decline for the virus titer is 3-log on the sodium pentaborate pentahydrate and triclosan solution-treated textiles, whereas the nontreated textiles do not show any decrease.101 This was confirmed by observing the cell deaths as a result of contact with the virus solution passed through the fabrics.

**TOXICITY AND ENVIRONMENTAL CONSIDERATIONS**

The use of metals and inorganic materials can present health and environmental risks. Bowkow and Gabbay conducted animal studies with antimicrobial and antiviral fabrics impregnated with copper to determine the fabric’s skin-sensitizing potential in both guinea pigs and rabbits.26 In studies that looked at exposure to these fabrics, no skin irritation was demonstrated over a 14 day period.26 Furthermore, Nohynek et al. reviewed the effects of TiO_{2} on the skin and found that there was little evidence to suggest that the use of TiO_{2} nanoparticles in cosmetics pose a risk to human health.102 However, Skocaj et al. reported in a similar review that the evidence for the safety of TiO_{2} in humans is still under debate, especially for its nanoparticulate forms.103 For example, Zhang et al. demonstrated that a culture of HFL1 cells treated with a 0.50 mg/mL suspension of TiO_{2} nanoparticles and incubated for 48 h experienced a 40% reduction in viability relative to control cultures using an MTT assay (for cell metabolic assessment).104

Research conducted by Hodek et al. performed cytotoxicity tests of their hybrid coating containing silver, copper, and zinc on Vero and HeLa cells, demonstrating viability values above 90% for both cell lines after 4 h.105 Similarly, the graphene oxide–silver nanocomposite created by Chen et al. successfully immobilized AgNPs to prevent toxicological effects and reduce potential downstream environmental impacts caused by free AgNPs.34 Additionally, some research has suggested that AgNP exposure induces metabolic arrest rather than cell death and that human cells have greater resistance than other organisms, providing some justification for their use for healthcare.105,106

Polyethyleneimine compounds have shown minimal cytotoxicity in mammalian cells.78 A study by Shi et al. evaluated the cytotoxicity of polyethyleneimines through an MTT assay on 3T3 mouse fibroblasts, showing no statistically significant difference between the polyethyleneimine-treated surfaces, untreated surfaces, and growth culture medium.107 Furthermore, photosensitizer materials such as rose bengal, which have been implemented in wipes, have also shown no toxic effect on mammalian cells.97

The impact of metal nanoparticles on the environment has been a concern since their popularity increased due to antimicrobial activity without the possibility for resistance.36 The mechanism of toxicity for nanoparticles is through association with the cell surface, dissolution of material by releasing toxic ions which impair enzyme function or DNA, or generation of ROS leading to oxidative stress.108 Recent studies have considered the environmental toxicity of the fabrication of these nanoparticles. In the study conducted by Li et al., copper nanoparticles were generated via a biosynthesis method, which incorporates vitamin C to avoid the toxicity of ROS created when CuNPs are exposed to air.111 Additionally, strategies have been considered which will reduce the environmental impact of nanoparticles, such as negative surfaces on nanomaterials to reduce cell surface interactions, capping of nanoparticles to reduce dissolution via toxic ions, and tethering of antioxidant molecules to nanoparticle surfaces to reduce ROS impact.112
EMERGING TECHNOLOGIES AND FUTURE PERSPECTIVE

In the previous sections, we introduced antiviral agents and coatings that have shown antiviral effects. Although these technologies have been effective in inactivating viruses on various surfaces, they still suffer from several shortcomings that inhibit their practical application for use in daily life. Most of these methods are not universal, and their effectiveness depends on the type of the virus. In addition, they might require long incubation times with the attached viruses that could contribute to the interim transmission of the virus. Challenges with mass production and material cost are other drawbacks to many of these technologies, including polyethyleneimine-based antiviral coatings and nanoparticle-based antiviral solutions. In this section, we introduce potential emerging technologies that could be used stand-alone or in combination with the currently available antiviral technologies to provide synergistic effects for creating antiviral surfaces (Table 3).

Pathogen-repellent surfaces, rather than surfaces impregnated with microbicides, have shown great promise for preventing bacterial adhesion and biofilm formation; however, there is limited information on the applicability of these surfaces in repelling viruses. These repellent surfaces are mostly inspired by natural systems and involve combining nanostructures, microstructures, and chemical functionality. Bioinspired hierarchical micro- and nanostructures have been shown to demonstrate antimicrobial effects, while also preventing the binding and attachment of pathogenic organisms to the surface in the first place. Due to the unique wetting properties/states of hierarchical structures, many biological contaminants have been shown to have poor adhesion to these surfaces. This has been most commonly seen with complex fluids such as blood, as well as with solutions containing bacteria, showing low surface contamination and bacterial growth. Nanostructuring of surfaces is a bioinspired technique that researchers regularly employ to obtain self-cleaning characteristics and varying levels of repellency. Similar to the lotus leaf and pitcher plant providing inspiration for self-cleaning surfaces, insect wings have inspired a nanostructured approach for antimicrobial capability. In addition to this, combining the chemical modifications, micro- and/or nanostructures with an infused liquid layer, mimics the effect of the pitcher plant, thus creating a class of surfaces called lubricant-infused surfaces. These surfaces have displayed superior performance in suppressing blood contamination and clotting while also preventing the growth and attachment of bacteria and their biofilms. Figure 6a shows the growth of planktonic bacteria biofilm after 21 days of incubation on dissolved oxygen-permeable membranes with and without a lubricant-infused coating. Although lubricant-infused surfaces show superior properties for pathogen repellency compared to other technologies, the stability of the lubricant layer, especially on surfaces open to air, is a current drawback of these coatings that could be addressed by choosing more stable lubricants.

Recently, nanostructured surfaces were tested by Hasan et al. for the purpose of antiviral capabilities (Figure 6b). Studying the impact of wet etching with NaOH on aluminum alloy Al 6063, it was found that rhinovirus-16 (RV-16) was very susceptible to loss of viability over a 24 h period, showing a 3- to 4-log reduction. The same research revealed a lesser impact on the viability of respiratory syncytial virus 4 (RSV4), with the virus naturally showing reduction after 24 h on Al 6063 alone, though significant decreases were recorded after just 2 h when nanostructures were present.

We recently developed a flexible omniphobic wrap featuring hierarchical structures (i.e., multiple length-scale structures) with repellent properties toward a multitude of fluids and pathogenic bacteria, including Staphylococcus aureus and Pseudomonas aeruginosa, as well as inhibition of biofilm formation on the surface (Figure 6c). To evaluate the repellency, a pathogen transfer analysis was demonstrated with GFP-expressing E. coli contaminating the repellent wrap and a commercial wrap through a simulated touch experiment (Figure 6c). The repellent wraps showed a significant reduction in the transferred bacteria between surfaces. In another work by Chauhan et al., cotton fabrics were modified with hexadecyltrimethoxysilane (HDTMS) to create a superhydrophobic and durable surface. To investigate antimicrobial effects, these surfaces were incubated with E. coli (1 × 10⁵ CFU/mL) at 37 °C for 24 h, and E. coli was unable to bind to the surface, resulting in cell death and the formation of an inhibition zone around the treated substrates.

Mannelli et al. demonstrated the effect of wetting properties on the stability of influenza A on glass surfaces treated with various hydro- and fluorocarbon chain length silanes. Three wetting condition combinations were considered: hydrophilic/oleophilic, hydrophobic/oleophilic, and hydrophobic/oleophobic. They were able to demonstrate the degradation of the viral envelope in the latter two cases, with the hydrophobic/oleophilic surface showing the largest amount of viral inactivity, an 80% reduction in viral activity, whereas for glass, there was little to no reduction in the virus activity. These emerging natural pathogen repellent/inactivating technologies could potentially be used for preventing viral contamination of high-contact surfaces in various settings.

Other emerging materials that utilize micro- and nanostructures to create antimicrobial effects are being investigated and developed using safe compounds while still displaying promising antimicrobial properties. For example, solid and mesoporous silica nanoparticles (SSN and MSN, respectively) functionalized with glycosaminoglycan (GAGs) have been implemented to attract viral glycoproteins and eliminate virus entry to host cells in solution. This method could provide a close proximity for virucidal agents to act on the virus, providing a dual functionality (i.e., capture and deactivation). The electrostatic and hydrophobic interactions between the GAGs and the virus (e.g., HSV-1 and -2), along with the facility of surface functionalization and biocompatibility of silica nanoparticles, make this system a promising method for eliminating infection in solution. This effect can be seen with the plaque reduction assay run on both HSV-1 (Figure 6d(i)) and HSV-2 (Figure 6d(ii)), which both displayed significant antiviral activity compared to the control case. Microwired SiO₂ particles (SiO₂ MPs) were also used for antiviral studies in solutions where the surface of the SiO₂ MPs were treated with APTES to add C₆₀ to their surface as a photosensitizer. Under blue LED light at a wavelength of 470 nm, these particles showed antiviral behavior. These treated particles could potentially be coated onto existing surfaces to confer antiviral properties.
| Material and Structure | Antimicrobial Testing | Promising Features | Challenges | Ref. |
|------------------------|-----------------------|-------------------|------------|------|
| **Nanostructured Aluminum** | Respiratory syncytial virus (RSV) | Pseudomonas aeruginosa | Dual action of antiviral and antibacterial | Limited to aluminum surfaces | 128 |
|                       | Rhinovirus (RV)       | Staphylococcus aureus | 3- to 4-log reduction in viability counts of RV within 2 h | Nanostructures are not controlled during fabrication | |
|                       |                       |                   |            |      |
| **Nanostructured Anatase—Rutile-Carbon (NsABC) Coating** | N/A | Escherichia coli | Photocatalytic activity was shown to present in UV light (4-log reduction in EOP, over 4 h), visible light (3-log reduction), and in the dark (2-log reduction); these results broaden the possible applications to everyday environments | Did not investigate durability; currently only grown on stainless steel surfaces | 51 |
| **Hierarchical Micro- and Nanostructure Based on Thin Film Wrinkling on Plastic Shrink Wraps** | N/A | Staphylococcus aureus | Reduces biofouling for bacteria | Requires heating to temperatures of 145°C to conform around an object/surface. | 2 |
|                       |                       | Pseudomonas aeruginosa | Flexibility allows them to be used in both medical devices or as medical surfaces |            | |
|                       |                       | Escherichia coli | Extremely durable, maintained its repellent properties after washing in solvents and hot water; simple manufacturing method; inactivation of E. coli via inhibition zone started showing after 12 h and continued up to 24 h | Does not investigate why the inhibition zone is created by the hydrophobicity or how the chemical modification would work on other fabrics | 129 |
| **Hexadecyltrimethoxysilane (HDTMS) Modified Cotton Fabric** | N/A | Escherichia coli | Liquid-infused surfaces |            | |
| **Fluorosilane-Based Omniphobic Lubricant-Infused Coating on Permeable Membrane** | N/A | Planktonic bacteria | Significantly reduced the formation of biofilm growth and formation of a 21 day period | Did not investigate potential antibiofouling effects on pathogenic bacteria | 125 |
| **Tethered-Liquid Perfluorocarbon Surface** | N/A | Pseudomonas aeruginosa | Pseudomonas aeruginosa was grown in coated PVC medical tubing for 6.5 weeks and showed an 8-fold reduction in the formation of the biofilm; the surfaces also reduced blood related biofouling | Reduction of biofilm in vitro only lasted 24 h; lubricant layer can evaporate over time resulting in the loss of performance | 5 |
| **PTFE Membrane Infused with Perfluoropolyether** | N/A | Staphylococcus aureus | PTFE lubricant-infused substrates showed 99.6% decrease in biofilm formation in a 7 day incubation under flow, for S. aureus, showing a 96−97.2% reduction for the other two pathogens in a 2 day period | Lubricant layer can evaporate over time, resulting in a loss of performance | 119 |
| **GAG Mimetic Functionalized Solid and Mesoporous Silica Nanoparticles (SSN-SO3 and MSN-SO3)** | N/A | HSV-1 and HSV-2 | GAG mimetic MSN and SSN act as a viral-binding inhibitor that inhibits HSV 1 and 2 from infecting cells within 1 h | GAG modification is attractive toward viruses, so it should be combined with an antiviral modification | 130 |
| **Poly(N-Benzyl-4-Vinylpyridinium Bromide (BVP) Resin** | N/A | Enterovirus, HSV, poliovirus, and HIV conovirus and echovirus human rotavirus, influenza virus, human adenovirus, and Japanese encephalitis virus | Efficient removal of viruses from aqueous solutions based on pyridinium affinity for viruses; 64-fold reduction for HRV, 256-fold reduction for influenza A, 32-fold reduction Ad-37, and 16-fold reduction in JEV after 30 min | Toxicity was not discussed and means of use on various surfaces; this method is attractive toward viruses, so it should be combined with an antiviral modification | 132 |
| **Poly(N-Benzyl-4-Vinylpyridinium Chloride)** | N/A | Bacteriophage T4 | Efficient removal of viruses from air based on pyridinium affinity for viruses | A membrane was fabricated; addition of this material to existing membranes was not investigated; this method is attractive toward viruses, so it should be combined with an antiviral modification | 133 |
Table 3. continued

| material and structure | virus | bacteria | promising features | challenges | ref |
|------------------------|-------|----------|--------------------|------------|-----|
| Liquid/particle-based material | Staphylococcus aureus | E. coli | only showed antiviral effect on enveloped viruses; potential to add on surfaces was not explored | E. coli (poly(4VP-co-NVP)) quaternized with benzyl halides | 134 |
| | | | performed in solution, not tested against virus | | |
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various materials. Bio-Fence has fabricated chlorine-binding polymer coatings that are antimicrobial and antiviral. Once the surface is depleted, it can be coated again by spraying the chlorine, according to their Web site. SurfaceWise is another surface coating approved by United States Environmental Protection Agency (EPA) to have antiviral activity with a single application. Caliwel BNA coating, based on calcium hydroxide, has also been approved by EPA for its antiviral and antimicrobial behavior. BioFriend BioMask is another company with FDA approval that produces masks that are able to trap pathogens including viruses and inactivate them.

In the future, a combination of pathogen-repellent coatings with antiviral materials could create synergistic effects, through which the surface repels the majority of the viruses while the coated antiviral agents inactivate any attached viruses that have not been repelled, providing a double layer of protection against viruses. This could greatly reduce the number of pathogens transferred from fomites to person and then from person to person. The improved biocompatibility and lower toxicity of structurally engineered repellent materials would allow them to be used in a larger range of applications including the highly regulated food and medical industries.

Combining a spectrum of materials with different antimicrobial mechanisms is expected to lead to smart surfaces that attract, bind, and eliminate a multitude of pathogens. Finally, integrating simple and real-time sensing capabilities to these antimicrobial surfaces, in addition to mitigating the risk of transmission, could help in identifying the pathogens present in the environment and eventually aiding the public health authorities in managing infectious disease outbreaks.

CONCLUSION

Modification of surfaces to confer antiviral capabilities is an area that is ripe for investigation. With the current SARS-CoV-2 pandemic, there has been a rapid surge in the number of studies that focus on quantifying the survival of SARS-CoV-2...
on various surfaces.\textsuperscript{5,148,149} We anticipate that several of the technologies presented here could be used as surface coatings to reduce the spread of infectious diseases, including COVID-19, via surfaces. We petition researchers to apply a more systematic approach to their investigations in studying the antimicrobial properties of surfaces, rigorously testing each category of viruses—enveloped or non-enveloped, DNA-based or RNA-based—prior to making claims of effectiveness. Above all, it is imperative that research claiming antimicrobial capabilities becomes more accurate about effectiveness against viruses, only making these claims when viral studies have been executed. Surfaces capable of immediately repelling and/or inactivating pathogens are urgently needed, and it is now the responsibility of scientists, industry, and governments to work together toward this goal.

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S.M.I. and L.L. contributed equally to this work. T.F.D. and L.S. supervised and conceived the research. S.M.I. and L.L. designed and wrote the main manuscript text with help from T.F.D. and L.S. T.M. and R.M. contributed to specific sections. All authors contributed to editing the manuscript.

\section*{Notes}

The authors declare no competing financial interest.

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\section*{VOCABULARY}

\begin{itemize}
  \item Plaque assay, A method of viral quantification relying on the formation of plaque-forming units of infected (lysed) cells \textit{in vitro} after inoculation with a viral titer; plaque-forming units are counted manually and given in units of PFU/mL; alternatively, immunostaining targeting viral antibodies can be used to quantify viral activity, measured in units of focus forming units (FFU/mL); 
  \item Reactive Oxygen Species (ROS), oxygen-containing free radicals produced during photoactivity and a variety of metabolic processes; in excess quantities, cause oxidative damage to components of the cell, including lipid membranes and genetic material; 
  \item Bacteriophage, a virus that specializes in infecting and replicating inside bacteria; 
  \item Photocatalysis, a process in which chemical reactions are generated in the presence of light; in semiconductors, this can result in the development of electron/hole pairs and reactive oxygen species in the presence of oxygen-containing compounds; 
  \item Enveloped virus, virus whose outermost layer is an envelope derived from the host cell's plasma membrane and composed of phospholipids, lipoproteins, and glycoproteins; non-enveloped viruses are instead protected mainly by a shell-like protein capsid; all viruses possess a capsid, but not all are enveloped; 
  \item Electrospinning/spraying, related fabrication processes by which polymer solutions in an electric field are forced through an opening when electrostatic repulsion between droplets exceeds surface tension; electrospinning occurs when the droplets form a continuous stream; electrospaying occurs when the droplets separate; 
  \item Positive and negative-sense ssRNA, viruses that replicate using single stranded RNA may produce a strand complementary or identical to the genetic material produced in the host cell; positive-sense strands possess the same nucleotide sequence and may be directly translated into proteins, whereas negative-sense strands possess the complementary sequence.
\end{itemize}
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