Design strategies for antiviral coatings and surfaces: A review ☆

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ABSTRACT

The routine disinfection and sanitization of surfaces, objects, and textiles has become a time-consuming but necessary task for managing the COVID-19 pandemic. Nonetheless, the excessive use of sanitizers and disinfectants promotes the development of antibiotic-resistant microbes. Moreover, that improper disinfection could lead to more virus transfer, which leads to more viral mutations. Recently developed antiviral surface coatings can reduce the reliance on traditional disinfectants. These surfaces remain actively antimicrobial between periods of active cleaning of the surfaces, allowing a much more limited and optimized use of disinfectants. The novel nature of these surfaces has led, however, to many inconsistencies within the rapidly growing literature. Here we provide tools to guide the design and development of antimicrobial and antiviral surfaces and coatings. We describe how engineers can best choose testing options and propose new avenues for antiviral testing. After defining testing protocols, we summarize potential inorganic and organic materials able to serve as antiviral surfaces and present their antiviral mechanisms. We discuss the main limitations to their application, including issues related to toxicity, antimicrobial resistance, and environmental concerns. We propose solutions to counter these limitations and highlight how the context of specific use of an antiviral surface must guide material selection. Finally, we discuss how the use of coatings that combine multiple antimicrobial mechanisms can avoid the development of antibiotic resistance and improve the antiviral properties of these surfaces.

1. Introduction

The rapid and uncontrolled global spread of the coronavirus SARS-CoV-2 has resulted in serious consequences for global human health. Despite the full attention of the World Health Organization (WHO) and the international community toward controlling the spread, as of 22 March 2021, over 122 million cases and 2.7 million deaths had been reported globally [1].

The COVID-19 pandemic has demonstrated that broad-spectrum antiviral surfaces, personal protective equipment (PPE), and specialized sanitary materials are required for providing short-term protection against new infections. These first-line-of-defense strategies can buy enough time to develop virus-specific vaccines and antiviral strategies [2]. They can also help slow the spread of viruses and limit the propagation of new vaccine-resistant variants [3]. Effective use of these strategies and materials requires knowledge of basic viral structure and infection routes.

Understanding external microbial attacks on a host organism involves both the macroscopic interaction between organisms and the microscopic interaction between the virus and host cells. Viruses are particles that can only replicate by infecting a host cell and, therefore, cannot reproduce on their own [4]. Viruses are not considered to be 'alive' due to reliance on a host to reproduce and survive. Viruses are commonly identified through the Baltimore classification system according to the nature of the nucleic acids in the virion (DNA or RNA), the symmetry of the protein shell (capsid), the presence or absence of a lipidic membrane (envelope), and the dimensions of the virion and capsid [4]. One of the most used virus classifications is based on distinguishing enveloped and nonenveloped viruses. Corona virus is enveloped RNA (Fig. 1) entrapping non-segmented, positive-sense, single-stranded ribonucleic acid (ssRNA) and covered with club shaped glycoprotein [5].

Most antiviral surfaces aim to disrupt the virus envelope; thus, these surfaces target only enveloped viruses. Because bacterial membranes and viral envelopes are structurally similar [5], the transformation of antibacterial surfaces for antiviral purposes has been widely studied [6].

At a macroscopic level, a virus particle can only encounter a host through assisted locomotion, such as transport on water droplets moving

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in the air. Even after contact, humans have physical and immune system defenses to prevent the virus from infecting cells: dead skin layers, mucous layers, a harsh saliva environment, antibodies, and immune cells. All these parameters combine to reduce the risk of infection after a person is in contact with viral particles. Novel viruses, or those unknown to the individual's immune system, can more easily cause infection because the host's immune system cannot recognize the pathogen. By avoiding detection, the virus can encounter a nonimmune host cell and pass into its extracellular matrix [4].. At the microscopic scale, the viral infectious cycle can now be divided into discrete steps: (i) attachment of the virus to the cell, (ii) entry of the virus into the host cell, (iii) production of viral mRNA and its translation by host ribosomes, (iv) viral genome replication, and (v) assembly and release of the newly produced viral particles able to spread to other nonimmunized cells [4].

The most common transmission route for viruses such as SARS-CoV-2 is through respiratory droplets and aerosols exhaled from infected hosts [7]; however, most nosocomial pathogens can persist on inanimate surfaces for weeks or even months, and results have become available regarding the long-term stability of SARS-CoV-2 on various surfaces for tens of hours to even 7 days [8]. Moreover, nonenveloped viruses can also undergo fomite transmission [9], and the proper disposal of infected wastewater, surfaces, disposable objects, and PPE remains an environmental and sanitary concern [10]. "High-touch" surfaces are manipulated repeatedly by people and favor the spread of diseases through the fomite transmission route (Fig. 2).

During viral outbreaks and in long-term care and health-care settings, numerous stringent regulatory protocols exist for sanitizing work and public spaces. These protocols include the routine cleaning and disinfection of surfaces and objects to slow or eliminate the transmission of viruses and microbes. The efficacy of these time-consuming procedures could be improved if these surfaces possessed intrinsic self-disinfecting properties. Such self-sanitizing surfaces would also reduce the amounts of applied disinfectants, bleach, and sanitizers, thereby lowering the risk of developing more resistant forms of these pathogens [11].

This risk of greater microbial resistance has become a serious concern over the last decades. The WHO declared antimicrobial resistance (AMR) as one of the top global public health threats facing humanity, requiring the development of antimicrobials that are effective against drug-resistant fungi, bacteria, and viruses [12]. Thus, when developing engineered self-disinfecting antiviral surfaces, it is important
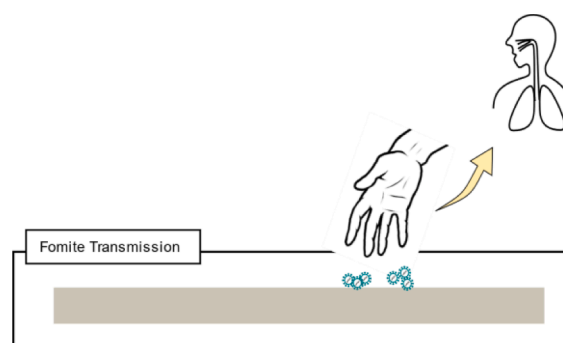

Fig. 2. The fomite transmission route through frequently touched surfaces. A virus-contaminated surface is touched by an individual who experiences self-inoculation after touching the contaminated surfaces and then transfers the virus to their face region.

to properly design the active compounds to avoid any uncontrolled development of AMR.

Here we review the most commonly used and advanced technologies related to antiviral surfaces. We present their respective mechanisms of action, point out limitations to their application, and provide a tool to simplify the selection of material for designing future antiviral coatings.

1.1. Review structure

Previous review articles on the current state of research related to antiviral materials and surfaces relied either on antimicrobial materials as a starting point [13] or on therapeutics and tools to inactivate SARS-CoV-2, for example [14]. The COVID-19 pandemic has encouraged collaboration within the scientific community to develop various antiviral materials. Despite this heightened interest in these surfaces, available data focuses mainly on antibacterial applications rather than antiviral ones; this bias stems in part from the complexity of viruses and their structure, elements that remain not fully understood at the molecular level [15].

Previous reviews have confirmed that inconsistent nomenclature adds complexity to any literature review. For this paper, we define the following: 1) antimicrobials are materials, substances, and compounds able to destroy or inhibit the growth of pathogenic microorganisms; 2) antibacterials relate specifically to antimicrobial items or approaches
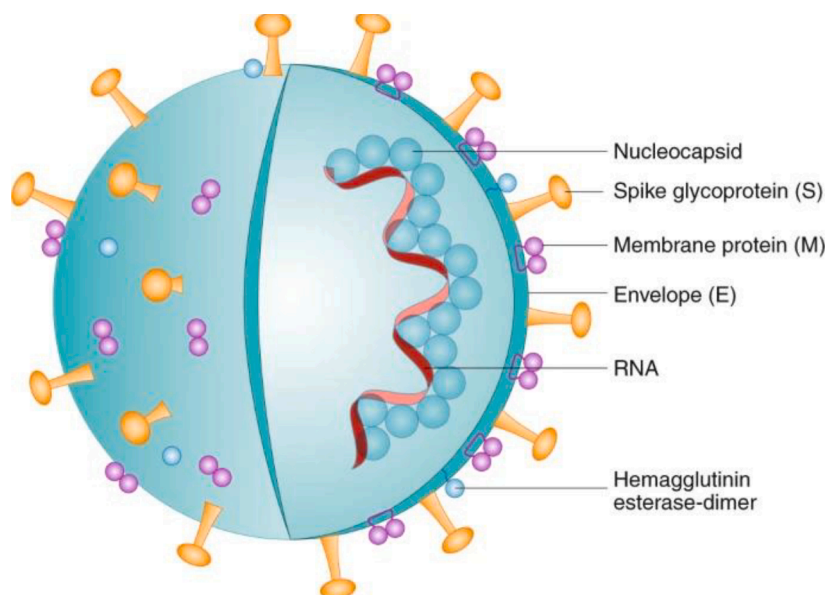

Fig. 1. Schematic representation of an enveloped SARS-CoV-2 structure [5].

that are effective against bacteria; 3) and antivirals relate specifically to viruses. We also use antibiofouling, antifouling, and antivirofouling in this review to define the ability of surfaces in preventing the adhesion of microbes and extracellular polymeric substances, including proteins, DNA and RNA..

Following the research engine methodology used in [16], we applied Boolean logic to search for published papers registered on Scopus. We conducted our search on 18 March 2021. We defined the research terms using two terms per search to include both antimicrobial nature and coating. We used the following terms: antimicrobial (antimicrob*), antibacterial (antibact*), biocidal (biocid*), antiviral (antivir*), anti-fungal (antifung*), anti(bio)fouling (antibiof*, antifoul*), coatings (coat*), and surfaces (surface*). In addition, we added the terms viru-cidal (viruc*) to include studies related to the antiviral properties of coatings and surfaces.

We found that the number of papers using the term "antiviral coating" or "antiviral surface" was at least one order of magnitude less than that for papers using the term "antibacterial coatings" or "anti-bacterial surfaces." This difference also highlights a delay in the avail-ability of COVID-19–related studies investigating antiviral coatings and surfaces. A challenge cited in antiviral surface literature relates to the wide range of viruses used for testing and the large inconsistencies among testing protocols [17].

We present metal ions, oxides, and nanoparticles under their elemental name. Contrary to [16], we disregarded the search term related to stainless steel as many papers used stainless steel as a substrate for the coating, generating false positives. As our search in March 2021 took place during the initial COVID-19 outbreak period (2019–2021), we found that the greatest research interest focused on the use of qua-ternary ammonium compounds, metal compounds and chitosan for antimicrobial applications, and antibacterial and antiviral coatings and surfaces.

The most common approaches for developing antiviral coatings rely on metal compounds as antimicrobial active agents. Silver- and titanium-based materials are the most used metals, and some examples based on these materials are already commercially available. The 2020–2021 pandemic increased research interest into copper, which has an inactivation rate directly proportional to the percentage of copper in the alloy surfaces [18]. Nonetheless, large-scale use of copper-based materials during a pandemic could lead to toxicity and environmental concerns. For organic materials, quaternary ammonium compounds and natural polymers, including chitosan, peptides, and polycations, are currently the most investigated and used materials.

In the first part of this review, we describe the different protocols for testing antiviral properties. Inconsistencies found in the current litera-ture increase the difficulty when comparing studies and trying to un-derstand the mechanisms underlying the produced effects. Therefore, issues related to the use of very different nomenclature and standards will be discussed and highlighted, and we present new research avenues for the study of the antiviral properties of coatings and for developing standard protocols for the antiviral testing of hard and soft surfaces. In the second part, we discuss the various materials and strategies available for designing antiviral coatings. The reviewed approaches presented here are tools that can be used either alone or synergistically with existing approaches to obtain coatings having improved antiviral and antibacterial properties.

2. Testing protocols for antiviral surfaces

Walji and Aucoin [17] provide a critical review of testing protocols, focused mainly on copper- and inorganic-based surfaces. They highlight the lack of consistency among testing protocols and viruses tested. Because of this inconsistent approach, it is difficult to quantify the antiviral properties of surfaces and compare how such materials affect different viruses; this inconsistency complicates defining "broad--spectrum antivirals." Walji and Aucoin also discuss how some standards,

such as ASTM E2721 [19], are proposed by regulatory agencies but are not broadly used in the literature. A similar problem, although not included in their review, applies to the use of standard protocols, such as ISO 21,702 [20], that define the virucidal activity of polymeric and porous surfaces. ASTM E1838 is used to determine the virus-eliminating effectiveness of hygienic handwash and handrub agents using the fin-gerpads [21]. Moreover, The virucidal efficacy of a variety of formulated microbicidal actives include antiseptic liquids, disinfectant wipes, disinfectant liquids, disinfectant sprays, and sodium hypochlorite against SARS-CoV-2 and other coronaviruses on inanimate surfaces was evaluated were conducted per ASTM E1053–20 [22].

Haldar et al. published a protocol to produce a permanent antiviral coating and determine its virucidal activity [23]. Interestingly, their protocol has been cited and used more than the standardized protocols. For soft surfaces such as textiles, the standard protocol ISO 18,184 [24] is used in literature to assess the antiviral activity of textile products [25], .

All other testing protocols found in the literature vary greatly in terms of humidity, temperature, media, and virus species used, thereby rendering any comparison of results impossible. The use of more consistent strategies in the design of experimental protocols for the antiviral testing of surfaces remains a key requirement for comparing materials and their effects on different viral strains.

As some tested viruses are human pathogenic microbes, the need for biosafety labs and trained technicians to test viruses represents another hurdle in the development of antiviral materials [6]. During a pandemic, only a limited number of suitable laboratories and trained staff are available for virus-based testing protocols. A means of expanding access to, at the least, pretest materials against viruses is through the use of virus-like particles (VLP) to assess the antiviral activity of nano-materials. Viruses can be considered as nanoparticles; therefore, tradi-tional nanomaterial analysis protocols can be applied to antiviral testing. These include VLPs such as carbon dots [26] and gold-based compounds [27, 28], which are nanostructures composed of one or more viral structural proteins but that lack genetic material. These characteristics make them excellent models for studying the morphology and structure of viruses without the risk of pathogenicity or infectivity [29]. At present, VLPs are mainly used in structural studies of viruses and vaccine development; however, future applications could include the screening of antiviral materials during the production phase.

Virus models, such as VLP, simplify viral biology and provide a better understanding of virus particles for the nonvirologist. Using VLPs and physical, non-biological methods could help material scientists to implement, without the need of biohazard containment facilities, bio-logically safe techniques and technologies. This access would increase the global antiviral testing capacity for nontherapeutic applications and permit the initial steps of material production without the need for biosafety Level 2 or above laboratory facilities.

The first theoretical studies of viral adhesion to surfaces involved wastewater treatment and environmental applications for developing adsorbents in water treatment processes and favoring the adhesion of viruses to solid particles in natural waters [30]. Viruses have a surface charge dependent on the solution pH in polar media, such as water. The pH value at which the net surface charge is zero is the isoelectric point (IEP) and is a characteristic parameter of each virus that also determines its motion within an electric field [31].

Gerba [32] developed a theoretical model of virus adsorption to surfaces. In particular, he relied on the surface charge of a virus and the presence of alkaline or acidic groups and ionizing residues on the virus surface to build a nanoparticle-like model for the virus. His-studies showed that the virus IEP plays a major role in determining viral adhesion. A positively charged virus adheres easily to negatively charged surfaces. Physical methods, such as quartz crystal microbalance with dissipation (QCM-D) and atomic force microscopy (AFM), allow mechanical measurements of the nanoscale interactions between mi-crobes and surfaces [33]. Joonaki et al. applied this model to

SARS-CoV-2 to provide more perspective on using these methods and spectroscopy techniques for characterizing and understanding fomite transmission [32]. Their theoretical analysis demonstrated that pH (Fig. 3) and temperature can modify the viral adhesion to surfaces, and high temperatures render the adhesion mechanism unstable. Since this article focuses on respiratory human pathogens, it should be mentioned that the viruses of concern are active within the pH between 7.35–7.45 (physiological pH). This would be different for gastrointestinal viruses.

3. Design of antiviral coatings

The diverse range of antiviral testing avenues and inconsistent data among published results puts emphasis on the need to improve our understanding of virus-engineered surface interactions. Despite these issues, we can categorize the antiviral materials used in coatings into two main categories: organic and inorganic compounds.

Organic compounds, such as polymers, can be used as coatings [23] or as matrices for composites [34]. Antimicrobial fillers for the polymer coatings include nanomaterials with antimicrobial properties, such as metal compounds [34, 35] or graphene-based materials [36]. Metallic coatings as fillers have also produced good results [37].

The key aspect in developing antimicrobial coatings involves the liquid–solid interface between the applied protective coating and the media on which viruses, fungi, and bacteria proliferate. The first step, therefore, is to study the coating's wettability. Surfaces having specific rugosity patterns can be defined as superhydrophobic (contact angle >150°) or slippery, and these properties are applied in the production of self-cleaning surfaces. Various hypotheses exist regarding the possible antiviral effect of superhydrophobic and slippery surfaces, including that the surfaces repel the microdroplets that serve as vectors of infection [38]. Many microbes having hydrophobic envelopes and membranes, however, can adhere to superhydrophobic surfaces [39]. To counter this viral property, researchers have evaluated superhydrophobic coatings and alternative strategies to obtain antiviral functional coatings [39]. In the following sections, we discuss the antimicrobial mechanisms of superhydrophobic surfaces, polycations, metal compounds, graphene-based materials, and photocatalytic particles.

3.1. Superhydrophobic antimicrobial surfaces

Most viruses, as well as bacteria, travel in water droplets from one host to another or from one host to an inanimate surface immediately prior to fomite transmission. Superhydrophobic or slippery surfaces, when properly designed, can reduce the contact area between water droplets and coatings and thus decrease microbe adhesion. The contact angle, defined by Young's equation [39], provides a measure of a surface's hydrophobic/hydrophilic behavior. When the water contact angle is 0°, wetting is complete, and the interface between the solid and liquid environment is maximized. On surfaces having water contact angles greater than 150°, the droplet maintains its spherical shape, and the liquid/solid interface is minimized [40].

The latter surfaces are suitable candidates for self-cleaning and self-disinfecting materials that can reduce bacterial adhesion [41]. Two factors contribute to the design of superhydrophobic surfaces and coatings: surface roughness and surface chemical composition [42].. Low surface energy materials, such as fluorinated compounds, are commonly used to chemically increase a coating's hydrophobic behavior [42]. A rough surface is then required to attain higher contact angle values [43, 44]. When the droplet lies on a rough surface, the water–surface system can be modeled as a droplet on a patterned surface. The most commonly used models are the Cassie–Baxter and Wenzel. In the Cassie–Baxter regime, the patterned surface comprises solid pillars and air [45].

Fig. 4a and b illustrate the concept of the self-cleaning behavior of the smooth and the superhydrophobic surface. In contrast with a smooth surface (Fig. 4a), the water droplet on a Cassie–Baxter surface shows a quasi-spherical shape (Fig. 4b). When the substrate is inclined, the water droplet rolls off. Contaminants, if present on the surface, are then easily picked up by the rolling water droplet [41] [46], and the superhydrophobic surface remains clean. These self-cleaning surfaces are defined by a droplet roll-off being able to remove any contaminant present on the surface at a tilting angle less or equal to 10° [41] [47].

Galante et al [42]. produced a polytetrafluoroethylene (PTFE)-based antivirofouling, nonwoven polypropylene coating thermally sintered to polypropylene (PP) microfibers; the microfibers created a robust rough surface. The coating produced a Cassie−Baxter wetting state on textiles; the surface area in contact with the liquid droplet was reduced by approximately 350 times relative to the control surface. These coated textiles demonstrated a 99.2% and 97.6% reduction in the attachment of adenovirus types 4 (HAdv4) and 7a (HAdv7a), respectively, relative to the uncoated controls.

To better understand the efficacy of superhydrophobic or self-cleaning surfaces when working with droplets containing bacteria or viruses, we must incorporate microbial activity within a micro/nano-structured surface. Several studies have demonstrated the limitations of adding micrometric rugosity patterns for antibiofouling purposes.
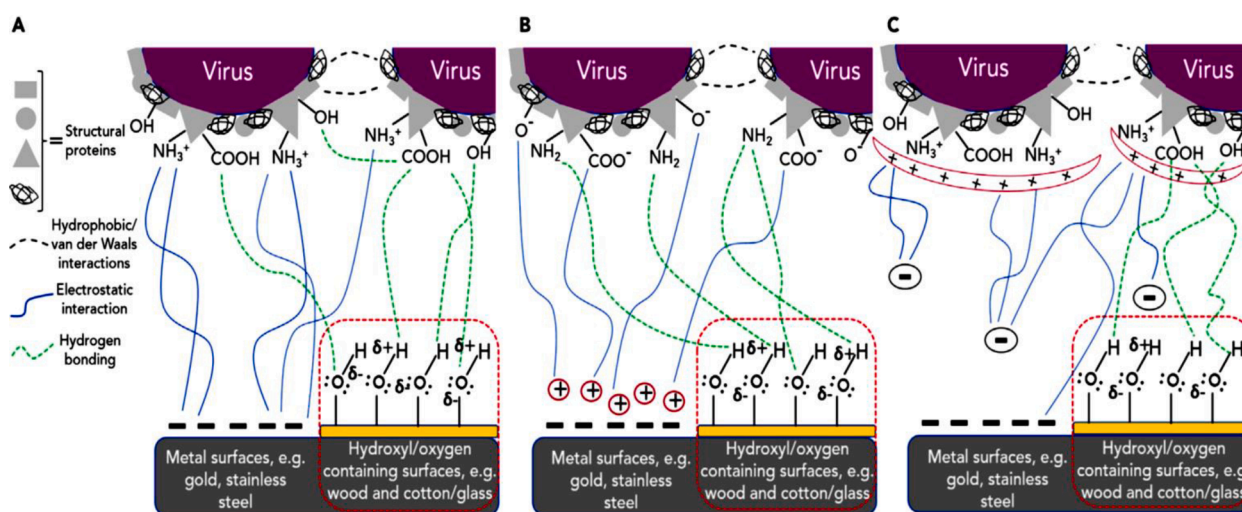

Fig. 3. Model of the potential molecular interactions between viruses and various surfaces; (A) a relatively low pH environment below the isoelectric point; (B) a relatively high pH condition above the isoelectric point in the presence of external ions (e.g., salts); and (C) well below the isoelectric point in the presence of potential surface sanitizing chemicals and a negative surface charge [33].
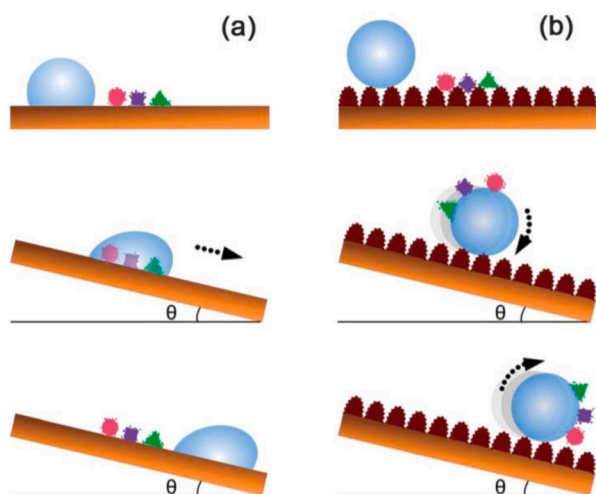
Fig. 4. Schematic illustration of the self-cleaning mechanism: (a) a smooth surface and (b) a Cassie–Baxter surface. When a standard smooth surface is tilted, the water droplet does not pick up the contaminants, whereas on a Cassie–Baxter surface, the round-shaped droplet removes the contaminants [41].

Bacteria can adhere to air microbubbles along the surface and proliferate within the roughness grooves [43, 44], thereby creating a favorable environment for further microbial colonization on the surface (Fig. 5).

More advanced approaches are required to counter this issue through the combined use of antimicrobially active compounds, such as cationic polymers (Fig. 6) [48] or metal nanoparticles (Fig. 7), to implement contact-killing strategies in the coating and maintain a rough surface topography characterized by self-cleaning properties. Surface hydrophobicity and oleophobicity decrease the abundance of attached microbes, and the active compound intervenes as a disinfectant to kill microbes that remain attached to the surface. This combination enhances the coating and maintains a superhydrophobic surface while also inactivating or killing microbes attached within the micrometric grooves.

3.2. Cationic polymers

The contact-killing mechanism is promising as this approach does not rely on the release of the active compounds. It can also be achieved through different measures, the most common being the grafting of polycations on the surface. Polycations can be natural (e.g., chitosan) or synthetic (e.g., polyethyleneimine (PEI)). Interactions of bacteria and viruses with polycations occur mainly because of their electrical charge. Most organic compounds having biocidal activity are polycations, which

can bind to the microbes' membranes or capsules through their active sites. This leads to the adsorption and penetration of polycations into the protective layer causing membrane disruption, the leakage of intracellular material, and the degradation of proteins (Fig. 8) [50].

Understanding these lipidic membrane/capsule–polycation and contact-killing interactions involves remembering that, for viruses, the surface charge depends strongly on the environmental pH and the viral isoelectric point (IEP). The IEP, defined as the pH value corresponding to no net surface charge, is unique to each different virus (Fig. 9) [31].

Polycations interact with viruses and microbes through the anionic sites on the virus envelope and the bacterial cell membrane. Whereas the isoelectric point can vary depending on the virus, polycations are generally more effective at a higher pH where the net charge of the virus is negative. A second mechanism of action of polycations is the chelation of important metals and nutrients, thereby preventing nutrients from entering the cell owing to the electrostatic interaction of metals with the cell wall [53, 54].

The antimicrobial mechanism of electrostatic interactions does not depend solely on the pH of the system but also on the number of polycation active groups. Song et al [48]. produced a fluorinated polycationic textile coating via chemical vapor deposition. Their results demonstrated contact-killing activity against both gram-negative and gram-positive *bacteria*, with viability reduction of 99.9%. In addition, the coating inactivated the negatively charged lentivirus-EGF as a virus model and showed good biocompatibility toward mouse NIH 3T3 fibroblast cells.

Another example of a polycation is chitosan, a partially deacetylated linear polymer of N-acetylglucosamine obtained by the deacetylation of chitin [52, 53]. In an acidic medium, N-acetylglucosamine groups are protonated, giving a positive charge to the chitosan molecules. Chitosan achieves this by behaving as a polycation in solution [54]. Chitosan exhibits antimicrobial activity owing to the electrostatic interaction between the protonated NH_3^+ groups and the negative residues on the cell membrane, presumably by competing with metal cations for interaction sites on the membrane surface [55,56]. These interactions affect the bacterial structure by altering membrane permeability, thereby provoking an osmotic imbalance and cell leaking [53].

Because chitosan is derived from chitin through deacetylation, i.e., the removal and substitution of acetyl groups with reactive amino groups (single bond NH_2), the degree of deacetylation (DDA) determines the content of free amino groups in the structure. When DDA is increased, there are more reactive amino groups and a higher potential antimicrobial efficacy [57].

Materials able to disrupt the cellular envelope as a principal antiviral mechanism offer a solution that is only effective against enveloped viruses. A study of the murine norovirus, a nonencapsulated virus affecting mammalians, demonstrated antiviral activity only after adding another antiviral agent into the chitosan film [51], illustrating how nonenveloped viruses are more difficult to disrupt using traditional
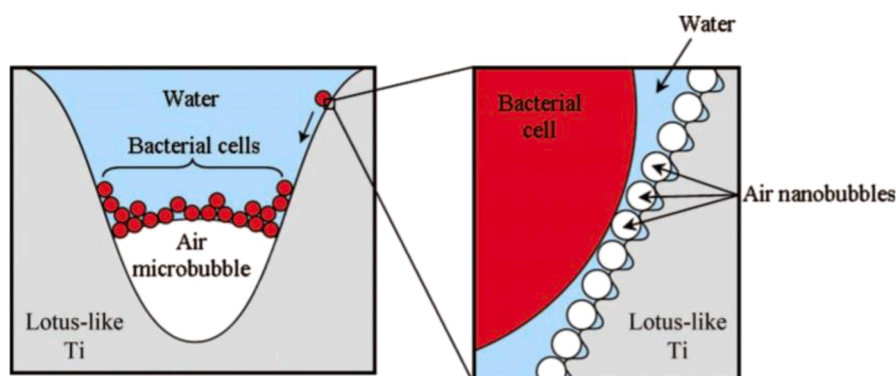

Fig. 5. Model for the colonization of microstructured superhydrophobic surfaces by bacteria [44].
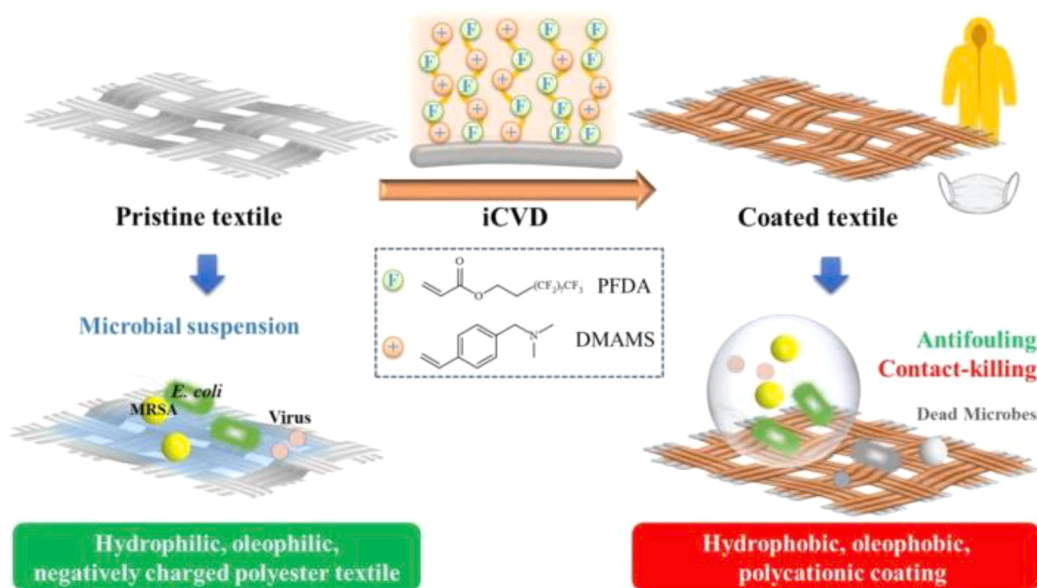
Fig. 6. Schematics of pristine textile functionalization with cationic polymers. In contrast to the pristine textile, the coated sample possesses antifouling and contact-killing properties [48].
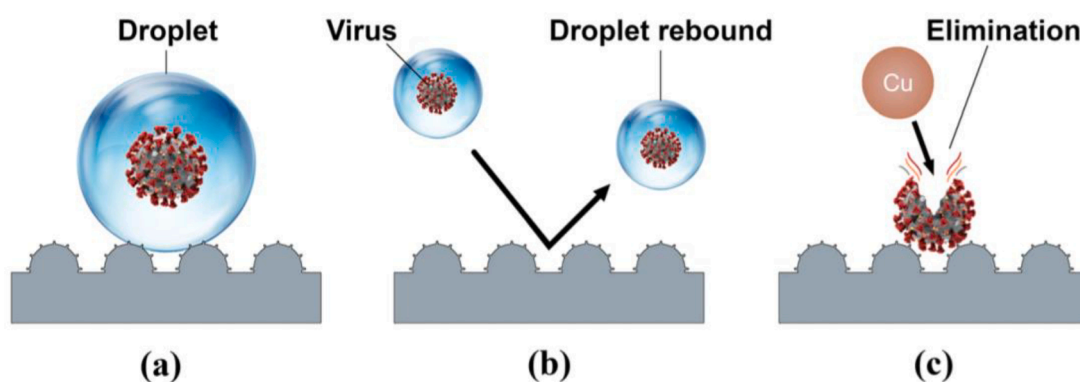

Fig. 7. Mechanism of action of a superhydrophobic surface having copper particles embedded in the coating: (a) a nonisolated droplet, (b) a rebounding droplet, and (c) copper inactivating the viral particles [49].
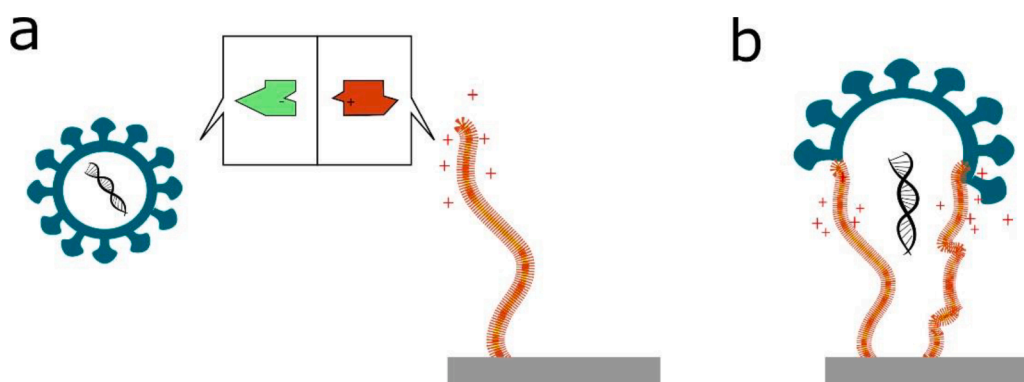

Fig. 8. Mechanism of action of polycations toward viruses; (a) the positive charge on the grafted polycation binds to the virus capsule; (b) capsule disruption and leakage of the viral material.

contact-kill antimicrobial methods that target the lipidic membrane, i.e., the viral capsule [58]. Materials with a quaternary amine moiety are known for their marked antibacterial [59, 60, 61] and antiviral properties [62]. He et al. synthesized and tested amino-modified chitosan against a Newcastle encapsulated virus; they observed the inhibition of virus transcription and the activation of an immune response [62].

The antiviral activity of chitosan within macroscale models has been, until now, investigated mainly for viral infections in plants. In plant
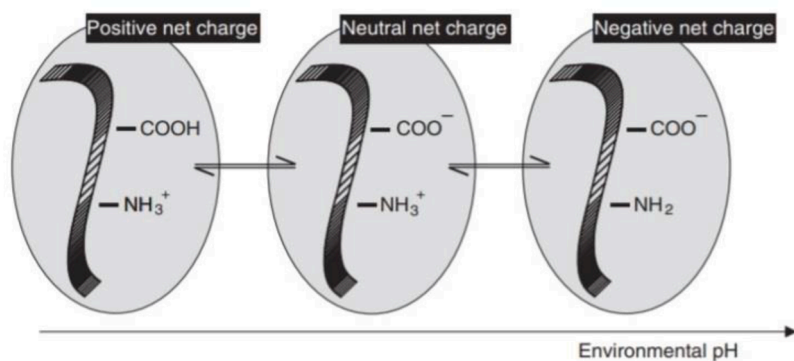
Fig. 9. Schematic representation of the viral isoelectric point. Increasing the environmental pH causes the virus to pass from a positive net charge to a negative net charge [31].

model studies, the main effect of chitosan is its ability to trigger an immune response rather than an ability to inhibit viruses. When in contact with chitosan, the plant recognizes chitosan as a phytopathogen; this recognition induces a wide spectrum of protective reactions and leads to the development of a systemic acquired resistance [63]. Similar results have been demonstrated in animal models testing the intranasal administration of chitosan against influenza A (H7N9) infection in a mouse model [64]; as with plants, chitosan triggered the immune defenses of the host organism. Given its ability to attach to epithelial cells, chitosan is also used as a vaccine and drug delivery carrier [65]; for example, it is used for topical applications of anti-hepatitis C drugs [66, 67]. Chitosan composites are therefore considered as promising materials for active food packaging [68, 69] and wound dressing [70, 71] applications.

Synthetic polycations are also gaining increased recognition. Kibanov's group has demonstrated how PEI immobilized on surfaces has antiviral properties for both enveloped and nonenveloped viruses [72, 73]. PEI has also been modified to produce different surface charge behaviors (neutral, cationic, and anionic) [74]. In this latter study, the cationic-modified PEI became 100% virucidal after 30 min of exposure. In contrast, the anionic-modified PEI demonstrated only a partial virucidal behavior, and no virucidal activity was observed for the neutral PEI. This difference is due to the presence of both positively and negatively charged sites on the viral membrane, although a greater amount of negatively charged ones [74].

Finally, given their intrinsic ability to stimulate the immune response, polycations are a valuable tool not only for their ease of application on substrates allowing the production of nonleaking antimicrobial properties but also for their action as immunostimulant adjuvant coatings for drug delivery systems to enhance the immune response of vaccines [75, 76].

Adding amine terminations to polycations can improve their antimicrobial activity, as shown using chitosan [77]. Quaternary ammonium compounds (QACs) are already well known and were initially accepted by the regulatory agencies for their use as commercial sanitizers and disinfectants. As with polycations, various approaches can be applied to have QAC bond covalently to surfaces [78, 79]. Immobilized QACs are hyperbranched polymers can serve as coatings having viricidal properties against enveloped viruses [80], such as the herpes simplex viruses [81, 82]. When used against nonenveloped enteric poliovirus, they found no significant viricidal properties, confirming that the QAC mechanism of action is mainly through disruption of the lipidic membrane [82].

It is also important to highlight that polycations and QAC surfaces are inactivated in protein-rich environments, such as plasma or serum, owing to competition between the proteins and viruses for targeting the QAC active sites [83]. The major drawback of non fixed QACs to the surface relates to antimicrobial resistance. Increased evidence is

emerging of co-resistance and cross-resistance between QACs and other common antibiotics and disinfectants [84, 85].

4. Metal-based compounds

Metal-based compounds are the most commonly studied materials of novel antiviral treatments. The main identified antimicrobial mechanisms are reactive oxygen species (ROS) production, lipidic membrane disruption and peroxidation, alteration of protein structure and function, and direct DNA and RNA damage [88, 89]. We will review here the most common metals under study: silver, zinc, copper, and titanium.

One of the biocidal mechanisms of metals is the release of the associated metallic ions and their interactions with bacteria, fungi, and viruses [86, 87, 88]. For silver, this process is considered as relatively slow under normal conditions and leads to low effective silver ion concentrations because of the low solubility of silver particles. Silver salts are therefore normally preferred for obtaining a higher local silver concentration at levels that can kill bacteria [89, 90]. Silver salts, such as silver halides and silver sulfide, have low solubility in water but produce a more controlled release of metal ions [89–91].

Silver compounds are normally better suited for humid environments compared to other metals. In fact, zinc and copper compounds can also be used as antiviral materials. Copper, in the form of CuO_2, has been shown, through a contact-killing mechanism, to inactivate viruses in its solid state and within a low humidity environment [92].

The positive charge of the metallic ions promotes an interaction with the negatively charged sites on microbes (Fig. 10). This interaction alters membrane structure, increases permeability, and produces reactive
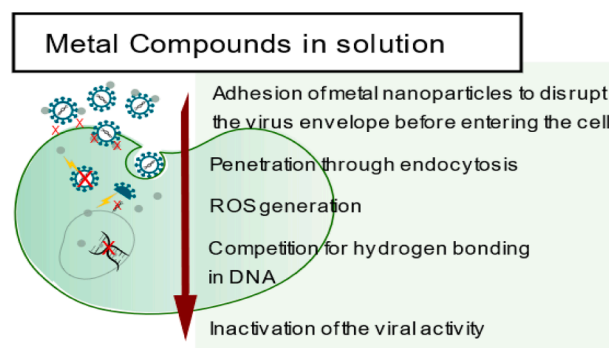

Fig. 10. Mechanisms of action of metal compounds in solution during the virus infection cycle. In a standard infection cycle, the viral particles i) adhere to the cell wall, ii) penetrate the cell through endocytosis, iii) release their viral content, and iv) replicate their viral RNA. The virus then enables the cell to v) assemble and vi) release new viral particles. Metal compounds can interfere with steps i, ii, and iv, to interrupt the infection.

oxygen species (ROS), which affect DNA replication and virus–cell interactions [90, 91]. For example, the antibacterial activity of ZnO compounds is well known; however, their precise antimicrobial mechanisms remain uncertain. Possible mechanisms include the direct contact of ZnO structures with cell walls [93,94], metal ion release [95], and ROS formation [96–98].

Antiviral composite coatings containing silver [99, 100], copper [101–103], zinc [104] or a combination of these metals have begun to be developed and tested. The main issue to overcome when embedding biologically active compounds into polymer coatings is ensuring that the active sites are present on the surface to ensure an interaction with microbes. As a process optimization approach, particles can be deposited on the partially polymerized coating to enhance interactions between microbes and nanoparticles .

The lack of availability of active sites for the direct contact with microbes can normally be addressed by adjusting coating thickness, filler content, polymer crosslinking, or adopting alternative pathways. For example, Behzadinasab et al [105]. proposed a simple approach based on a two-step deposition to avoid inhibition of the antiviral properties of CuO_2 by the polymer matrix. The first layer was a polyurethane (PU) coating that was partially cured on the surface. This was followed by a second step whereby CuO_2 nanoparticles were applied on top of the non-fully cured PU. The nanoparticles were thus partially embedded within the surface, keeping the CuO_2 accessible to microbes [105]. This approach produced a reactive coating demonstrating a strong antiviral activity against SARS-CoV-2 with an efficacy maintained after both mechanical damage and washings. Šlamborová et al [104]. produced a methacrylate-based hybrid coating using silver, copper, and zinc cations through a sol-gel route. This solution, which requires a short curing time at room temperature, resulted in a highly efficient, low-cost process suitable for industrial-scale applications.

The drawback of using some metal-based compounds is the leaching of metal ions, which is necessary for the antimicrobial activity of the metals. These applications are therefore less environmentally friendly than other contact-kill solutions. Much scientific debate remains about possible associated environmental and toxicological issues that have yet to be addressed or fully understood [106–108]. Embedding nanoparticles within polymer matrices could, however, eliminate some of these concerns, as this approach reduces the leaking of metal ions and cytotoxicity while maintaining an antimicrobial effect [104]. Silver nanoparticles, for example, can be PEGylated to decrease their cytotoxic effects and increase their antiviral activity [109].

4.1. Photocatalytic materials

Metal oxides, such as TiO_2 or CuO, are well known for their photocatalytic properties. Once exposed to UV, these materials can produce ROS and develop antiviral efficacy [110–112]. Nakano et al [113]. produced a TiO_2 thin film through spin-coating. They demonstrated how the inactivation of the influenza virus depended on UV-A light intensity and showed that by increasing UV-A light intensity, inactivation efficacy increased. The level of UV-A intensity in their experiment presented a good model of daytime indoor intensity. One drawback to these materials is that they are ineffective in the dark, under visible or fluorescent light, or under low-intensity UV light. To describe the antiviral mechanism, Nakano et al. evaluated the degradation of proteins and RNA. After 16 h of irradiation, all viral protein fragments were fully degraded, and the quantity of viral RNA was reduced by 90%. These findings indicated that these surfaces first attacked the viral envelope and then damaged the nucleic acids (DNA or RNA).

Other works confirmed this double-acting antiviral mechanism whereby the degradation of proteins took place because of strong oxidization mediated by OH and O_2—produced by TiO_2 photocatalysis [114]—and photocatalytic damage by TiO_2 that likely targeted the nucleic acids [115].

The main drawback of these materials is their selectivity for incident light wavelengths. Many studies have focused on the functionalization of TiO_2 nanoparticles to increase their reactivity in the visible range [116, 117] or under fluorescent light [118] to improve the antiviral activity of TiO_2 in indoor conditions, i.e., low UV Fig. 11. illustrates TiO_2 functionalization to improve antiviral activity. After functionalization with Cu(II), the nanoparticles photogenerate holes that produce ROS and thus provide an antiviral effect under visible light conditions. In the dark, the presence of reactive Cu(I) metal nanoparticles ensures an antiviral effect due to the Cu contact-killing properties.

5. Graphene-based materials

Graphene-based materials have demonstrated antimicrobial properties both in their reduced form, such as graphene nanoplatelets (GNP) and reduced graphene oxide (rGO) [119], and their oxidized form, i.e., graphene oxide (GO) [120–123]. Being 2D materials, platelet shaped nanomaterials have both micrometric properties on the surface and nanometric properties on the thickness. Due to these physical properties, graphene materials act as nano-knives on lipidic membranes because of their sharp nano-edges [124, 125]. The structure of graphene-based platelet-shaped materials allows the sharp edges to puncture the membrane (Fig. 12). Chemical residues on GO materials enhance this effect by inducing ROS generation.

Graphene-based materials, such as GO, rGO, and GNP, have begun to be used as components of nanocomposites with metal nanostructures covalently attached to or grown directly on the graphene-based materials [94, 126].

The proper design of composites using those materials takes advantage of the associated nano-knife effect owing to the microscopic size of graphene-based materials while also adding the nanometric antimicrobial effects of the nanostructures grown on the graphene surface [126]. The micrometric size of GO, rGO and GNPs also ensures that the nanomaterials are more available on the surface of bulk polymer composite materials when used as fillers, whereas the nanomaterials eventually grown on the platelets are responsible for an increase in antimicrobial activity [127].

6. Conclusions

Testing is a critical step in antiviral coating design. Given the increased demand for antiviral testing, access to testing facilities is difficult for studies involving antiviral coatings. Material scientists should apply physical techniques, such as QCM-D and AFM, and comparison should be made with antiviral standard protocols to provide easy-to-reproduce, consistent data; our understanding of antiviral mechanisms would improve greatly improve with this standardization.

For the design of antiviral coatings, commonly accepted approaches
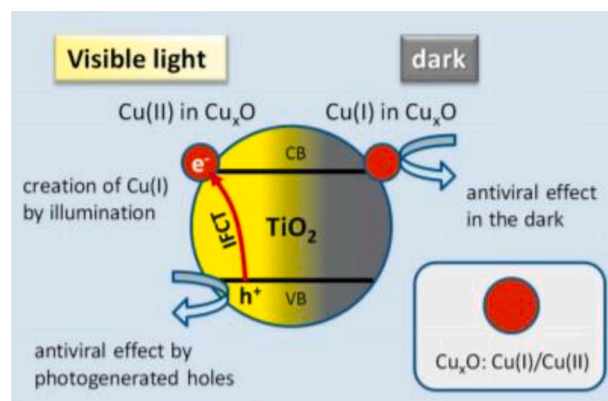

Fig. 11. Antiviral effect of a visible light-sensitive Cu_xO/TiO_2 photocatalyst [112].
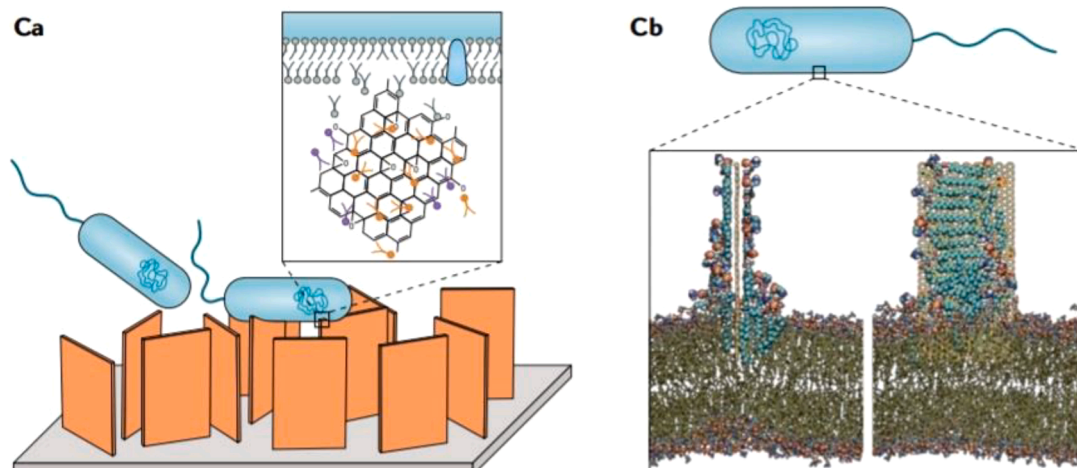
Membrane cutting by graphene nanosheets

Fig. 12. Mechanical damage of cell walls in contact with platelet-shaped graphene-based materials. Schematic (a) and molecular simulation (b) images of bacteria–graphene structural interactions in which the platelet behaves as a nano-knife on lipidic membranes [124].

include superhydrophobic surfaces, silver-, zinc-, or copper-releasing compounds, polycation functionalized surfaces, and photoactive surfaces.

An improved selection of material requires that attention be given to the application. Once pH, humidity, and light conditions of the final applications are known, antiviral coatings could be produced by selecting the material of interest; for example, photocatalytic materials should be used in the presence of UV radiation, not in dark conditions in which they are not expected to provide any antimicrobial effect. In a similar way, humidity can influence the selection of metal particles; for example, silver is most suitable for wet environments, whereas copper is better for dry conditions.

One main drawback of the widespread use of these materials involves a selection of AMR genes. Moreover, as their activity is based on a release mechanism, their activity will be reduced over time. Although high concentrations can extend their lifetime, these higher levels could also lead to the excessive leaking of toxic metal ions. Efforts to counter these environmental concerns are based mainly on encapsulation, which would reduce toxicity, control metal release, and increase the longevity of the coating.

Superhydrophobic surfaces can significantly decrease interactions between infected droplets and surfaces; without a coadjutant; however, these surfaces cannot offer antiviral activity against enveloped viruses. Interestingly, although superhydrophobic surfaces have an affinity for hydrophobic microbes, the same microbes are more easily targeted by polycations.

Polycation activity is highly dependent on the pH that protonates the protein chains and increases or decreases the interaction between the polymer and the microbe. In particular, pH also depends on the IEP of the protein that is to be targeted within the biological system. The main drawback of this kind of material is a shorter longevity owing to the accumulation of viral and bacterial debris from the disruption of the envelopes and membranes, respectively. These surfaces can normally be reactivated after proper cleaning [128]; however, the same cleaning must be investigated during antiviral testing.

Finally, during the material design, the targeted application and contextual environmental conditions (pH, humidity, light conditions) must be understood and integrated into the choice of materials. Subsequently, the combined use of two or more antiviral mechanisms likely offers the best means of ensuring optimal performance, and mechanisms that can work synergistically to inactivate viral particles are particularly encouraged. Efforts must be made to prioritize strategies that avoid AMR, as this microbial resistance represents one of the greatest challenges for modern medicine.

Declaration of Competing Interest

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

Acknowledgments

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