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Review

Antibacterial and Antiviral Functional Materials: Chemistry and Biological Activity toward Tackling COVID-19-like Pandemics

Bhuvaneshwari Balasubramaniam,[⊥] Prateek,[⊥] Sudhir Ranjan, Mohit Saraf, Prasenjit Kar, Surya Pratap Singh, Vijay Kumar Thakur, Anand Singh,* and Raju Kumar Gupta*

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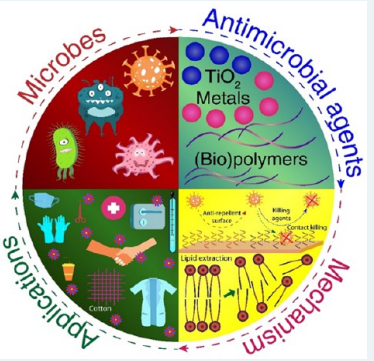
ABSTRACT: The ongoing worldwide pandemic due to COVID-19 has created awareness toward ensuring best practices to avoid the spread of microorganisms. In this regard, the research on creating a surface which destroys or inhibits the adherence of microbial/viral entities has gained renewed interest. Although many research reports are available on the antibacterial materials or coatings, there is a relatively small amount of data available on the use of antiviral materials. However, with more research geared toward this area, new information is being added to the literature every day. The combination of antibacterial and antiviral chemical entities represents a potentially path-breaking intervention to mitigate the spread of disease-causing agents. In this review, we have surveyed antibacterial and antiviral materials of various classes such as small-molecule organics, synthetic and biodegradable polymers, silver, TiO_2, and copper-derived chemicals. The surface protection mechanisms of the materials against the pathogen colonies are discussed in detail, which highlights the key differences that could determine the parameters that would govern the future development of advanced antibacterial and antiviral materials and surfaces.



KEYWORDS: *antibacterial, antiviral, COVID-19, polymers, nanomaterials*

INTRODUCTION

Nanotechnology plays a vital role in treating an expected and unexpected infectious diseases that are caused by bacteria and viruses.[1] In general, antimicrobial agents are chemical substances that are either bioactive polymer/synthesized polymer in combination with or without nanoparticles (NPs). In particular, antibacterial properties of NPs are widely proven and show a significant response even at lower concentrations due to their high surface to volume ratio.[2] Their function is mainly to act as an antimicrobial agent to inhibit the growth or kill the pathogenic *microbes*, namely, bacteria, fungi, and viruses. Recently, many organic compounds including polymers/biopolymers have shown potential as antibacterial and antiviral agents to tackle the infections caused by harmful bacteria and viruses.[2−4] Hybrid antimicrobial coating materials comprising copper, silver, and zinc cations have also shown great virucidal effects in controlling the severe viruses such as influenza H1N1, HIV-1, dengue type 2 viruses, and human herpesvirus 1. This excellent virucidal effects of these NPs make them excellent virucides to be applied in common surfaces toward tackling infection spread and disastrous levels of disease in the populace.[5,6]

The recent worldwide outbreak of the novel coronavirus (SARS-CoV-2) has resulted in more than 20 million people being afflicted with the disease and the virus is widely referred to as COVID-19.[7,8] This disease initially causes severe respiratory complications and can become life-threatening by disrupting the function of key organs. In 2003 and 2012, similar viral infections took hold among the human population which were named as a severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS), respectively.[9] Another deadly virus disease caused by Influenza A viruses claimed many people's lives and created a pandemic.[10] However, COVID-19 is considered to be more dangerous than other infections caused by coronaviruses because it is more contagious compared to other pathogens.[9] The knowledge about the mode of spreading of SARS-CoV-2 has been evolving since this disease was discovered, primarily because this virus is new to the human population and has spread fast. The action of this virus is complicated as it has undergone multiple mutations during all clinical trial efforts; hence, no medicine has yet been found to cure the diseases caused by this virus, despite worldwide trials.[11] Therefore, until suitable vaccines or therapies are available, preventative measures are of prime importance to curtail the spread of

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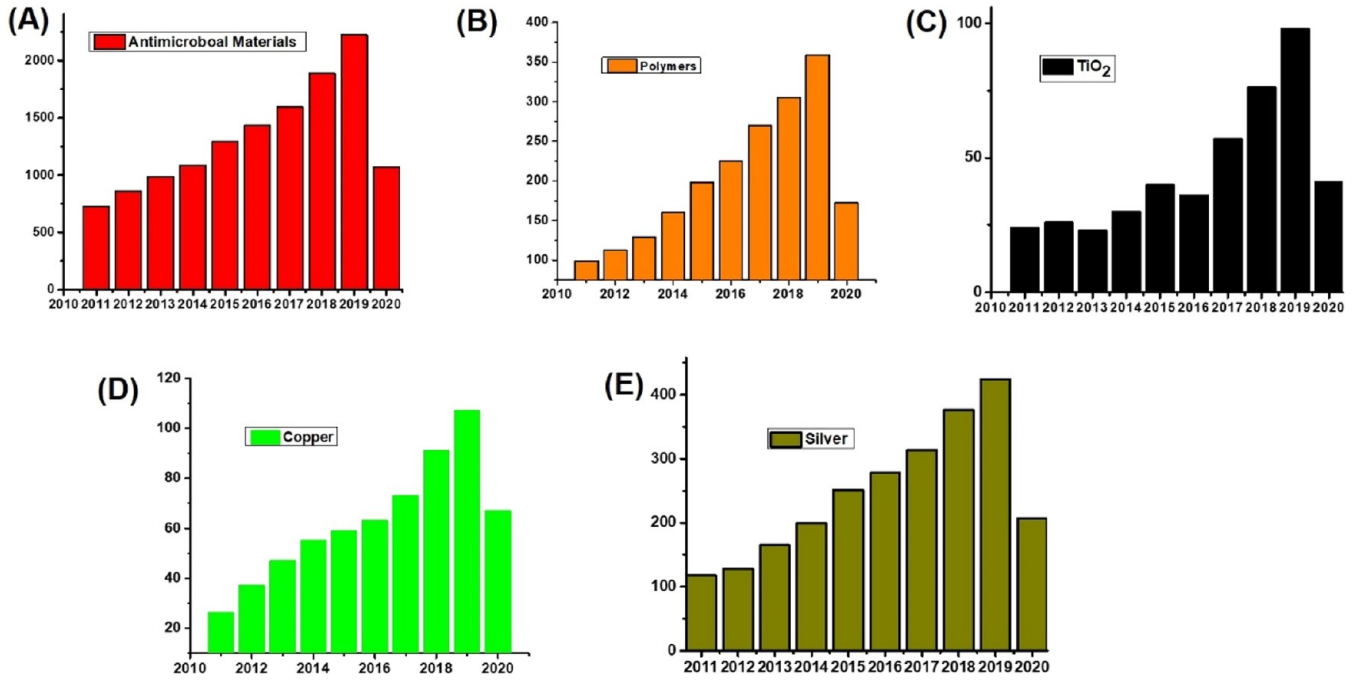

Figure 1. Web of Science data on published scientific papers on the (a) Antimicrobial materials and coatings, (b) Antimicrobial polymers, (c) TiO_2 based antimicrobial materials, (d) copper-based antimicrobial materials, and (e) silver-based antimicrobial materials; data accessed on June 20, 2020.

SARS-CoV-2. Toward this, a deeper understanding is necessary to safeguard everyone from the possible virus spread or infections which are believed to be mainly transmitted by touching contaminated surfaces and by being in the vicinity of exhaled droplets.[12−14]

Direct human to human transmission of the virus can be avoided by following physical distancing norms, wearing masks, and maintaining hygiene practices.[15] However, the other possible route for COVID-19 transmission is indirect contact, which is the biggest threat as it uses inanimate objects as pathogen reservoir/carrier to propagate the infection.[16−21] Common infected surfaces that could cause virus transmission are telephones, lift buttons, light and/fan switches, handrails, taps, and benches.[22] Once the virus is attached on hands, it gets transferred to eyes, nose, mouth as the virus is capable of living in air and on surfaces from hours to few days.[23] Significant literature data is available about the indirect transmission caused by human coronaviruses, namely, SARS-CoV-1 and SARS-CoV-2,[24] through aerosol media and from various surfaces,[25] i.e., cardboard, stainless steel, copper, plastic, and other healthcare-related materials available in hospital environments.[23] The lifetime of the coronavirus on stainless steel, plastic, aerosols, cardboard, and copper was found to be 72, 72, 3, 24, and 4 h, respectively.[25] In addition to this, there is a great concern for fungal infections, particularly hospital-acquired infections.[26] This type of healthcare-associated infections (HIAs) causes significant morbidity and mortality which brings additional enormous associated costs.[22] Also, the most susceptible people for HIAs are the immunocompromised patients, notably those suffering from AIDS.[27,28] Similar to bacteria, adherence of fungi to biotic and abiotic surfaces poses a challenge in the removal of the biofilm communities,[29] which further intensifies the severity of microbial infections. For example, one of the most common pathogen species called Candida causes hospital-acquired bloodstream infections in the United States, with around 400 000 cases a year worldwide, which are often associated with implanted medical devices.[27,30,31] Globally, the reported deaths due to antimicrobial-resistant infections is nearly 700 000 per year.[22] If new antibiotics are not developed to mitigate the rise of antimicrobial resistance, then by 2050, the world economy has to spend US$100 trillion on such infections and related issues which are predicted to affect the lives of more than 10 million people per year.[22]

Google Scholar data estimates that among the coronavirus related publications as of April 20, 2020, nearly 39 100 were published from the time of outbreak (January 2020).[32] Few reports and review papers summarized the clinical characteristics, epidemiology, pathogenesis, and COVID-19 management.[33,34] One of the modes of virus spread or any microbial community spread in healthcare environments is mainly through infections due to frequent touching of infected places, namely, doorknobs, switches, personal protective equipment, and wooden or plastic surfaces.[35] Hence, there is a need for techniques to prevent these surfaces from harboring *microbes* which can be through the use of antimicrobial/antiviral coatings. As prevention is a fundamental concept to combat or reduce the infections due to infected surfaces, there is an increasing need for identifying materials which possess antimicrobial/antiviral functionalities to minimize the spread of infections. Recent reports have summarized the design of engineered surfaces by forming self-assembled monolayers for the detection and prevention against SARS-COV-2.[36,37] Advanced development in the area of nanobiotechnology has led to the development of a variety of materials that have potential as antibacterial agents and biomedical catalysts.[38−40] Nanotechnology advancements have enabled researchers to control the physicochemical characteristics of metallic nanomaterials to develop suitable nontoxic antimicrobial drugs, which shows high potentiality in the medicine field.[41−43] In the

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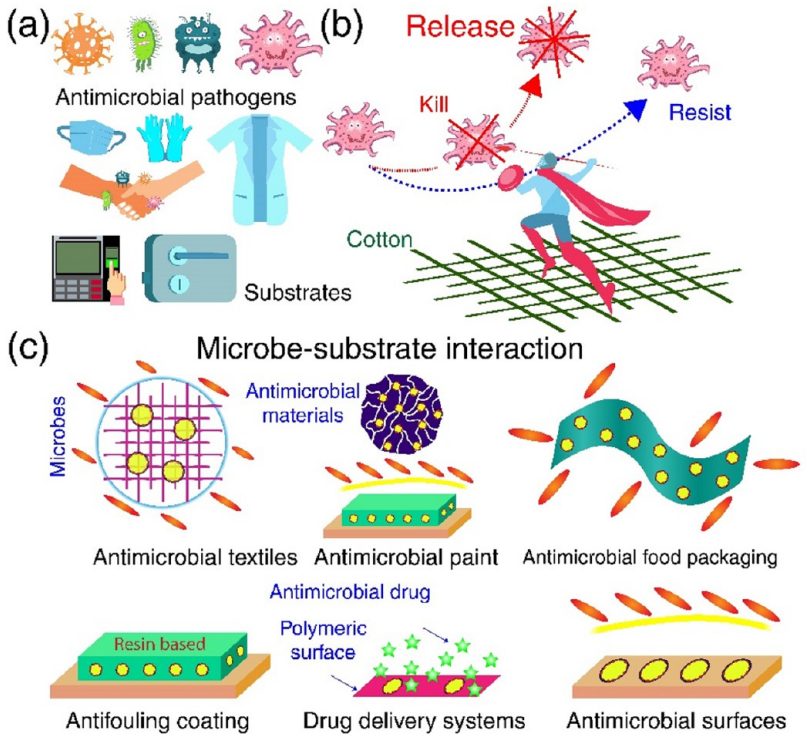

Figure 2. (a) Emerging antimicrobial pathogens. (b) Antimicrobial mechanism against the pathogens. (c) Antimicrobial coatings for various applications.

ongoing pandemic, antimicrobial metal NPs could be one of the effective solutions to address this issue. These NPs are active antibacterial agents due to their large active surface area which allows them to easily penetrate biofilms. Even before the pharmaceutical antibiotic revolution, some metals such as silver (Ag) and copper (Cu) were employed as antimicrobial agents. The progress in this field is continuous, and a new class of "nanometallo-antibiotics" has emerged which involves studying various NPs for their antimicrobial properties.[44−46] Beginning in the 19th century with the discovery of a direct correlation between the evolution of disease and pathogens, medical research has witnessed a paradigm shift on the focus of the development of metal-based antimicrobial agents. Furthermore, this resulted in several scientific types of research to study the antimicrobial effect of metallic copper and its compounds, which unlike silver is due to a faster and higher microbicidal efficacy shown by copper against pathogens in the ambient environment. Due to its biocompatible nature, TiO_2 is one of the most commonly used semiconductors for antimicrobial applications in contemporary literature. Therefore, few selective metallic or oxide NPs (copper, silver, and titanium dioxide (TiO_2)) which are superior and cost-effective in providing the antimicrobial properties through functional coatings are currently focused in this review. Detailed attention is paid to some of the important synthetic, natural, and biodegradable antimicrobial polymers which possess demonstrated functional characteristics as well as display rapid inactivation of a broad spectrum of microorganisms.[47]

Novelty. Keeping an eye on the current pandemic situation and its timely need to protect the surfaces which are unavoidable from day-to-day touch, we propose to bring out all the very basic information on antiviral and antimicrobial coatings and their applications. This review also highlights the perspectives of antimicrobial treatments mainly related to biomaterial surfaces or coatings. Furthermore, the estimated antimicrobial coatings market potential by 2021 would be US $4.19 billion with an additional compound annual growth rate of 12.1% considering it from the years 2016−2021.[48] Hence, the purpose of this review is to concisely present the application of important metal NPs and polymer-based materials on the contribution of antimicrobial coating formulations. Review articles related to functional characteristics and importance of antimicrobial coatings for preventing possible microbial colonization growth or spreads on vulnerable surface touches are rarely reported. The Web of Science data on antimicrobial materials for microbial repellent coatings and its potential applications are presented in Figure 1.

Recently, efforts are focused toward the development of smart and antimicrobial surface creations against the microbial related infections.[48−52] The conceptual diagram on the emerging pathogens (bacteria, virus, and fungi) and surfaces which are prone to microbial contamination such as those in hospitals and their relative mechanisms are presented in Figure 2a,b. The antimicrobial coating on various substrates depicting the microbe−substrate interactions is shown in Figure 2c.

SYNTHETIC ANTIMICROBIAL POLYMERS

As the demand for antimicrobial materials with superior disinfection properties is on the rise, the development of novel and human-friendly microbe-resistant polymer or polymer nanocomposites materials to fight against the microbial contaminations are of contemporary interest. While biomaterials are being employed for various applications, one of the adverse effects reported is the origination of bacterial adhesion with further biofilm formation on the biomaterial surfaces that can cause severe infections. Globally, the estimated biomaterial-related infections are mainly (64%) in the form of

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hospital-acquired infections compared to other types of infections.[49] To control this, there are two types of defense mechanisms created through antimicrobial coatings. In general, the antibiofilm mechanism which accounts for the surface protection is created based on antifouling or antimicrobial coatings. Antimicrobial polymers offer promising and enhanced efficacy among the available antimicrobial agents with the potential to minimize the healthcare and environmental related problems.[53−59]

Antifouling coatings prevent biofilm accumulation occurrence on surfaces through repelling or controlling the microbial biofilm architecture of surfaces.[55] In contrast, antimicrobial coatings work solely based on bacteriostatic or bactericidal activity.[55] The former is based on the mechanism of steric repulsion or nanoscale-based topographies, and the latter follows the mechanism of contact killing or by releasing the antimicrobial compounds or inorganic metal ions that causes cell death. On the basis of the antimicrobial activity and its related mechanism, the polymers are categorized as passive (repelling) or active (killing) materials.[56] The "repelling"-based mechanism is mainly from hydrophilic/hydrophobic and electrostatic repulsions and the low surface energy of the matrix. The "killing"-based mechanism is based on electrostatic and biocidal interactions. The logic of choosing materials to design antimicrobial surfaces and their engineering perspectives are thoroughly discussed in the latest review.[60] Discussions are made based on the past applications which made potential impacts on the antimicrobial surfaces for various applications.

Greater attention has been paid to the biocidal polymers because of their inherent properties such as nonvolatility, chemical stability, environmental friendliness, and durability, which make them advantageous over other polymers as antimicrobial materials.[55] The biocidal polymers are mostly polycationic thereby binding to the protein's membrane of the microbial cells effectively. Many cationic polymers have emerged as successful candidates in the recent past as antimicrobial substances. The majority are nonbiobiodegradable, thereby studies into their potential side effects to humans are necessary for ensuring the medical safety.[61] Biocidal polymers which are surface-active are generally described as surface-bound polymers, and the polymer which releases the biocidal substances in solution are called solution-bound polymer.[56]

The characteristics of antimicrobial polymers, methods for their synthesis, factors which affect their antimicrobial activities, and their major fields of application are extensively covered in the literature.[4,62] The toxicity of the conventional antimicrobial agents can be minimized by accompanying them with green antimicrobial polymers with the help of reducing agents thereby increasing their antimicrobial efficiency and selectivity.[62] Few polymers such as chitosan, quaternary-nitrogen-group-containing compounds, poly-ε-lysine (ε-PL), halamines, triclosan, and polybiguanides show an inherent capacity to display antimicrobial activity.[53,63−65] Additionally, they act as a backbone to incorporate small biocides and antibiotics.[53,66] Polyacrylate-based antimicrobial polymers, namely, polydimethylsiloxanes (PDMS) and 2-hydroxyethyl acrylate/acrylic acid, and an amphiphilic polymer, poly-[(aminoethyl methacrylate)-*co*-(butyl methacrylate)] (PAMBM), have already been evaluated for medical coatings.[67,68] The functional characteristics of quaternary ammonium salt siloxane copolymers and *N*-halamine siloxane have been studied for their use in biocidal coatings. The copolymer coating consisting of quaternary ammonium salt siloxane and *N*-halamine on cotton swatches exhibits biocidal efficacy against microbial colonies such as *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*).[69] Also, *N*-halamine-incorporated nonwoven fabrics have been used as antimicrobial materials against avian influenza virus and airborne bacteria,[70,71] and their action on the inactivation of the contaminated aerosol is shown in Figure 3a. These *N*-halamine

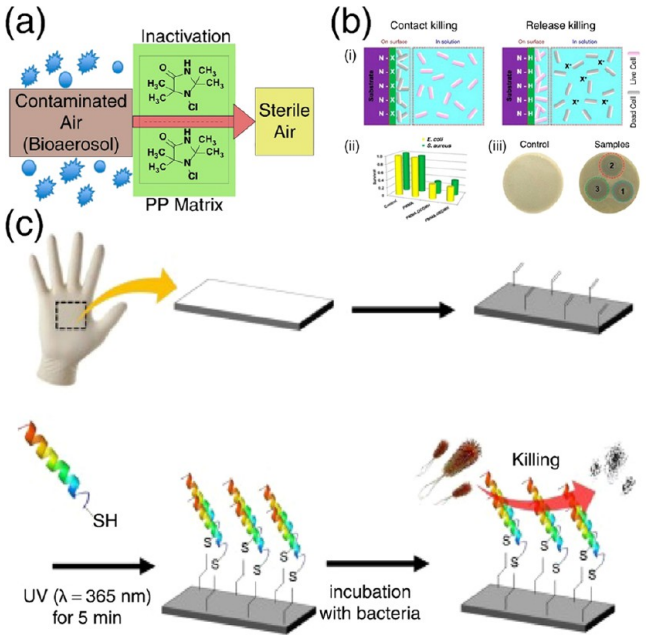

Figure 3. (a) *N*-Halamine antimicrobial mechanism against aerosol. Reproduced with permission from ref 71. Copyright 2015 American Chemical Society. (b) (i) Schematic illustration of an antibacterial mechanism for *N*-halamines against harmful bacteria. (ii) Survival of *E. coli* and *S. aureus* after contact killing assay of the control, pure PMMA, PMMA−DCDMH, and PMMA−DBDMH. (iii) Optical images of the inhibition zone against *E. coli* for the samples (1) PMMA−DCDMH, (2) PMMA−DBDMH, and (3) PMMA−DCDMH/DBDMH. Reproduced with permission from ref 66. Copyright 2016 American Chemical Society. (c) Overall scheme for polymer coating and AMP immobilization on the surface of the substrate. Reproduced with permission from ref 48. Copyright 2018 Elsevier.

materials possess superior antimicrobial properties against the wide spectrum of microorganisms such as yeasts, fungi, Gram-positive and Gram-negative bacteria, and viruses.[71] They have received significant attention during the past decade as antimicrobial materials due to their efficacy.[65,72] The contact and release killing mechanisms of *N*-halamine-incorporated electrospun PMMA fibers loaded with 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), have been established based on the studies conducted against the bacteria's *E. coli* and *S. aureus*.[66] Their action against the bacterial strains and the mechanisms involved in fighting against the harmful bacteria are shown in Figure 3b. Enzyme-embedded antimicrobial substances based on polycaprolactone (PCL) polymers with antibiotic gentamicin sulfate (GS) coimpregnation coatings have exhibited very good antibacterial properties. The test was conducted on three test isolates: *E. coli*, *S. aureus*, and *Pseudomonas aeruginosa* (*P. aeruginosa*). On the basis of the in *vitro* release studies, it was

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concluded that the PCL-GS polymeric materials can be effectively tunable as self-degrading antimicrobial biomaterial coating on catheters.[73]

Successful immobilization of Cys-linked SHAP1 peptide-based polymers (antimicrobial peptides (AMPs)) on the surfaces of a vinyl-functionalized glass slide and nonconventional latex gloves have been performed with the help of iCVD technology. A flow cytometry method was used to determine the antimicrobial efficacy of the coating developed. The immobilized antimicrobial peptides showed high antimicrobial activity, >96% against two typical pathogenic bacteria. The overall scheme for polymer coating and AMP immobilization on the surface of the substrate and the antimicrobial mechanism is described as shown in Figure 3c. On the basis of the various antimicrobial studies, it was concluded that the coating technique employed can be effectively developed further for various types of equipment and medical devices.[48] Polydopamine-based antimicrobial coatings have also gained significant attention in the past decade due to their flexibility for functionalizing all types of materials and universal biocompatibility;[74−78] however, the drawback is their instability in an alkaline environment.[79] Hence, with the right combination of functionalization or cross-linking with different materials, it is possible to attain the stability over the polydopamine coatings for various microbial environments.[75,80]

Conducting polymers such as polyaniline and polypyrrole have already proven their microbial resistance properties in many fields such as antifouling or antimicrobial coatings,[81−86] biomedical,[79,87−95] and food packaging.[96−101] Due to their superior properties against controlling the microbial colonization of various surfaces and the development of resistant microbe strains, they have been recently explored for disinfectant applications as well.[94] These polymers possess unique properties such as ease of synthesis on a large scale, excellent environmental stability, a tunable backbone ($-NH_2$) for tailoring as antibacterial materials, flexibility for functionalization, and doping.[102]

Ready to eat food packaging is contaminated with numerous viruses due to lack of proper antiviral packaging material. The viral pathogens transmitted from contaminated food packaging surfaces causes viral foodborne outbreaks.[103] There are a few commercial polymers already in use for the food packaging applications Novaron, Zeomic, AgIon, and Cleanaid.[104] Only limited information is available on the application of antimicrobial materials in the control of human enteric viruses as far as active packaging and food-contact surfaces with virucidal activity are concerned. For designing materials with antiviral properties, several factors need to be considered. Foremost is the intended application where the material is going to be used, as synthetic and biobased plastics like polyhydroxyalkanoates (PHAs) or polypropylene (PP) would be used in the case of the food-contact surface or food-packaging material applications. Furthermore, biopolymers such as proteins (zein and soy protein), lipids (beeswax), and polysaccharides (chitosan, starch, cellulose) are chosen for the coating of edible food products as they satisfy the safety criteria of having "generally recognized as safe" (GRAS) status.[103] The challenges posed on testing the materials for antiviral properties due to the higher rate of infection and transmission limits studies on the evaluation of antiviral materials. Hence the materials that have passed the antibacterial tests are considered for antiviral applications as well as with the further important testing measures. In general, the antiviral polymers are defined by comparing the virucidal activities of materials with and without viral loads for the intended applications with specific experimental conditions such as contact time and temperature. A promising strategy toward broad-spectrum antivirals is mainly to block or suppress the first step in the viral life cycle which is the entry of the virus and its traveling to the target cell.[105] Many synthetic polymers have been tested as antiviral drugs against viruses such as human immunodeficiency virus type 1 (HIV-1), influenza, herpes simplex viruses (HSV) types 1 and 2, varicella-zoster, papilloma, hepatitis B and C, and respiratory syncytial viruses, and the challenges have also been documented. Hence, with the limited trials and testing, it is always challenging to come out with functionally enhanced antiviral coatings for surface treatment with different emerging and re-emerging viruses contaminations.[105,106] Antimicrobial polymers with nanosized materials have been employed as antiviral coatings or sprays for controlling viral load on contaminated surfaces.[107]

Pyridinium-type polyvinylpyrrolidones with different counteranions were developed, and their antiviral activity was tested against influenza virus through a plaque assay technique. Studies reported that the polycations showed antiviral activity of 95.6% of virucidal efficiency. Antibacterial efficiency of the same material was tested against *E. coli* bacterial activity. It was concluded that the pyridinium-type polyvinylpyrrolidones play a dual role as both antibacterial and antiviral activities against a broad-spectrum of pathogens.[108]

A novel continuously active antimicrobial coating exhibited the ability to reduce the hospital-aquired infections (HAIs) in hospitals. The modified coating demonstrated greater residual efficacy against viruses. On the basis of the evaluation of the antimicrobial polymer coatings, it was found that the coated surfaces effectively acted against human coronavirus (HCoV) 229E. The virus concentration was reduced by greater than 90% in 10 min, and after 2 h of contact, it was reduced by greater than 99.9%. The same coating formulation in suspension showed an effectiveness greater than 99.99% against HCoV 229E in 10 min of contact. The outcome of this study yields an opportunity toward controlling the COVID-19 transmission from contaminated fomites.[109] However, more studies are needed to further evaluate the effectiveness of the proposed antiviral coating.

HAIs pose a greater threat and potential risk to patients, and one of the methods to reduce this risk is to use antimicrobial coatings or spray which can decontaminate the surfaces contaminated with pathogens, mainly bacteria/viruses.[110−114] In some cases, even after proper care is taken, recontamination is unavoidable due to the persistence of the pathogens.[115] Antimicrobial coating or spray can be of immediate relief against pathogens spread mainly from the HAIs. One such antimicrobial spray used a quaternary-ammonium-based polymer, which acts as a barrier for bacterial survival on surfaces for up to 15 weeks through surface bonding.[116] The bed frames, medical equipment, mattresses, walls, furniture, ceilings, doors, windows, curtains, and hallways can be cleaned using the same polymer coatings once the hospital room is cleaned.[112] It was discussed that the active ingredient present in the antimicrobial polymer reduces both bacteria and fungus or the microbial burdens. Although it does not kill spores, its influence on both surface charge and hydrophobicity enhances adhesion to surfaces which limits the spores being aerosolized or transferred to other surfaces.[112,117]

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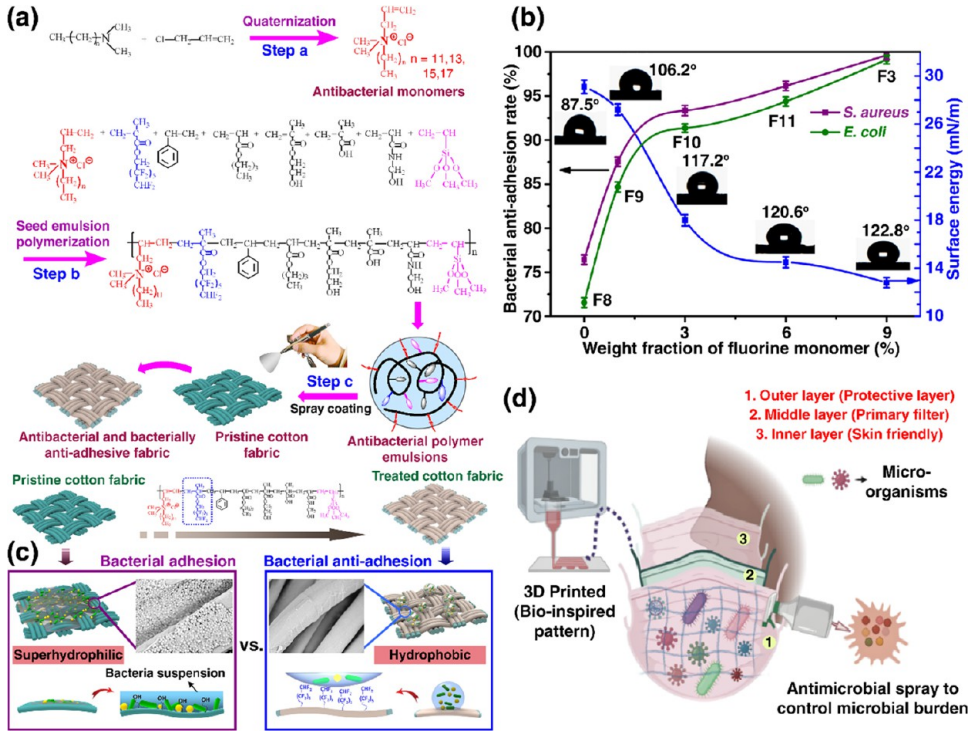

Figure 4. Antibacterial spray coating on fabrics. (a) Schematic of the synthesis route for the antibacterial and bacterially antiadhesive cotton fabric. (b) Bacterial antiadhesion rate, WCA, and surface energy of the antibacterial cotton fabrics (F8, F9, F10, F11, and F3, representing the different weight percentages of fluorine), with different amounts of fluorine component. (c) Comparison of the bacterially adhesive and antiadhesive action model of the pristine and treated fabrics. Reproduced with permission from 85. Copyright 2018 American Chemical Society. (d) Conceptual design of antimicrobial mask with 3D printed filter. Created with BioRender.com.

Antimicrobial Polymeric Coatings on Fabrics. Recently, cotton fabrics have been coated with different types of polymers or polymeric nanocomposites materials to achieve a permanent antimicrobial characteristic without compromising their physicochemical and mechanical properties.[85,118−125] Here, we present one of the examples from ref 85. The antibacterial and polymeric monomers from alkyl-dimethyl tertiary amines based monomers (ADTA-X) were prepared via a quaternization reaction by reacting them with 3-chloropropene. The antibacterial polymeric emulsions concerning different alkyl chain lengths were prepared through a seed emulsion polymerization route, and the as-prepared emulsions were spray-coated on the thoroughly cleaned cotton fabric, as shown in Figure 4a. Different characterizations were employed to understand the antibacterial and antiadhesion properties against two different bacteria, namely, *S. aureus* and *E. coli*. The durability of cotton fabric with antibacterial polymeric coatings was also presented. Scanning electron microscopy (SEM) studies of polymer-coated fabric confirm the reduction of bacterial adhesion compared to that of pristine fabric. It was stated that the polymers with the fluorine component helped the coated fabrics to attain greater antibacterial activity. Bacterial adhesion on a surface is generally very difficult to assess as it is a complex process which is governed by many factors such as (a) bacterial cell surface properties, (b) the aqueous or liquid environment, and (c) material surface properties. On the basis of that fact, the role of the fluorine component on increasing the rate of bacterial antiadhesion on the fabrics was tested using a water contact angle (WCA) test. The results show the trend of the increased rate of bacterial antiadhesion of the antibacterial fabric with increased hydrophobicity. Also, less adherence of bacteria was noticed on the coated fabrics. Hence, it confirms the role of the fluorine component in increasing the hydrophobicity of the antibacterial polymers, as shown in Figure 4b. The mechanism behind the antiadhesion properties of the fluorine-incorporated or grafted polymer was discussed. The hydrophobic segments of the fluorine component facilitated the in-depth penetration of the hydrophobic segments present in the polymer chain into the lipid domains of the membrane which lead to the membranolysis and cell death. Thus, bacterial colonization was prevented, resulting in enhanced antibacterial capability. The dose of the fluorine component determines the rate of hydrophobicity of the antibacterial polymers. The schematics representation of antiadhesion properties of the pristine and antibacterial-coated cotton fabric is shown in Figure 4c.

Although few studies reported that hydrophilic surfaces prevented the bacterial adhesion compared to hydrophobic surfaces,[126,127] most authors advocated for the hydrophobic surfaces for antiadhesion of bacteria, especially with regard to *in vitro* environments.[128] As it has been proven that antibacterial fabrics help in inhibiting or destroy the bacteria and microbe's growth, deeper attention needs to be paid for developing antimicrobial fabrics, thereby reducing transmission of infectious diseases in hospital-related environments. As 3D printing technologies are gaining significant attention in the biomedical forum,[129] it would be interesting to adopt 3D printing technology in designing mask, personal protective equipment, and gloves. The polymer-nanocomposites-based membranes, based on a bioinspired design, can be printed as filter material to control the microbial burdens infusion. The design concept for preparing a protective mask with a 3D-printed bioinspired polymeric filter for controlling the microbial burden is illustrated in Figure 4d.

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Superhydrophobic Coatings. The interest in superhydrophobic coatings expressing antimicrobial activity has gained momentum in the recent past. The term superhydrophobicity is coined based on the lessons taught by nature, i.e., the "lotus leaf" effect, which attracts a plethora of unique opportunities and functional applications in the field of microbial-repellent coatings, specifically in the medical field. This superhydrophobicity concept depicts the self-cleaning of surfaces and repelling of any microbial adhesion, thereby preventing surface contamination. So, the creation of superhydrophobic surfaces impacts its widespread use as easy-to-clean surfaces with the autocleaning effect. Fine-tuning the surfaces plays a major role in providing advantageous functions to this surface. There are two features of the surface as measured by the contact angle (θ), such as hydrophobic and hydrophilic characteristics, which define the surface properties. According to Young's equation, in general, the ideal wetting property of a smooth surface is defined based on the contact angle: If the contact angle is 0°, then the wetting of the surface is complete, whereas a contact angle of 180° indicates the nonwettability of the surface as the droplets stand on the surface itself. Similarly, the surface is hydrophilic if the contact angle is less than 90°, and it is hydrophobic if the contact angle is greater than 90°. The surface with a contact angle higher than 150° termed as superhydrophobic surface. The major factors which influence the surface wetting properties are its roughness and chemical composition. To mimic the lotus leaf surface with hierarchical micro-/nanostructures plus a waxy hydrophilic film, it is necessary to fine-tune the surface contact angle to higher than 119°, where higher surface roughness plays a major role. The mimicked heterogeneous wetting (Cassie−Baxter model) property of the surface helps in the reduction of adhesion force between the water droplet and surface. Thereby, dirt or any microbial adhesion on the surface is completely cleaned and taken away by rolling off of water droplets with a slight tilt of the surface. This was the motivation behind the development of bioinspired superhydrophobic materials for antimicrobial coating.[55] The successful repulsion and removal of microbial colonies, such as *E. coli*, *Streptococcus mutans*, *P. aeruginosa*, and *S. aureus* or any Gram-positive or Gram-negative bacteria, from different superhydrophobic surfaces have been carried out,[130−138] which shows the importance of superhydrophobic surfaces or coatings for antimicrobial repellence.

Smart Antifilms. Recently, a new generation of antibacterial strategies is developed to overcome the shortcomings of conventional antimicrobial methods.[49,139,140] They are originally conceptualized as surfaces with smart antibacterial and antibiofilm characteristics as they release drugs on-demand with respect to environmental signaling or triggering by external stimuli, thereby preventing biofilm formation or total damage of the matured film, respectively. The external stimuli mentioned here for creating smart surfaces are mainly electricity, temperature, light, magnetism, and induced redox changes. Hence, the antifilm is a growth-restricted biofilm (or) otherwise dissolved completely into the solution as biofilm formation is terminated.[49]

Although many polymers are used for synthesizing and creating antimicrobial coatings for various applications, ensuring biodegradability and biocompatibility are the major criteria, particularly when used for biomedical applications. Furthermore, the innate cytotoxicity of synthetic polymers is a major drawback for their application in medical devices, despite their proven efficiency against microorganisms.[48] Hence, the need of the hour, antimicrobial application, relies totally on the development of biopolymers and biodegradable polymers. Detailed discussions on the progress of biopolymers and biodegradable polymers in antimicrobial applications are given in the following section.

■ ANTIMICROBIAL BIOPOLYMERS

With advancements in technologies, plastic-based products are becoming a prime source of pollution. The rising demand and consumption of conventional plastics have created great concern for humans, animals, and the environment. These are prime sources of environmental pollution. The global primary plastic production reached 407 million tonnes in 2015, with a waste generation of 302 million tonnes. Plastic waste handling involves three primary techniques, namely, landfills, incineration, and recycling. However, the recycling, incineration, and discard percentages were low, i.e., 20, 25, and 55%, respectively, in 2015. Thus, plastic waste recycling requires serious attention toward a sustainable future.[53,141,142]

Thus, there is an urgent need to look for biodegradable and renewable sources of polymers.[143] One of the main biodegradable polymers is cellulose, having the inherent advantages of hydrophilicity, biocompatibility, biodegradability, and low cost. Their biomedical applications arise from an important feature of hydrophilicity, owing to the hydroxyl, aldehyde, and carboxyl groups, and making a facile preparation of hydrogels.[144,145] Cellulose also offers a sustainable means for superhydrophobic coatings having several functionalities. The overall advantages are the excellent durability, simplicity, environmentally friendly, and ease of scale-up.[146,147]

Why are Natural Products Needed? Although various synthetic materials have been developed for microbe-repellent surfaces, natural and renewable-source-based antimicrobial surfaces are urgently needed for controlled microbial growth and reduced activity. Recently, the focus has shifted from synthetic polymers to biodegradable polymer surfaces because of degradation in the presence of moisture and temperature without emission of any toxic byproducts. The key challenges are good mechanical strength, chemically inert, environmentally friendly, biocompatible, thermally stable, low cost, and abundantly available.[148] The potential candidates are polysaccharides, e.g., starch, cellulose, agar, and chitosan, and proteins, e.g., casein.[149−151] The following section will critically review the newly developed natural microbial repellent surfaces.

Natural-Product-Based Antimicrobial Materials. Different biobased antimicrobial surfaces can be broadly divided into two main categories, viz., polysaccharides and proteins.[152] The next subsections will cover the mechanistic details of their antimicrobial performance.

Chitosan. Chitosan, a biopolymer discovered by Henri Braconnot in 1811 upon deacetylation of chitin, a natural and most abundantly available polysaccharide after cellulose. Later, Charles Rouget extensively worked on chitosan until 1859, and the name was coined by Felix Hoppe-Seyler in 1894. Chitin and chitosan are found in fungi cell walls, insects, mushrooms, and the exoskeleton of crustaceans. The research on different applications of chitosan started in late 1970, and later was applied in the pharmaceuticals area in the early 1990s, followed by extensive research in the therapeutic system. Chitosan finds applications in various fields such as agriculture, textiles, pharmacy, food industry, and cosmetology.[153,154] A linear and

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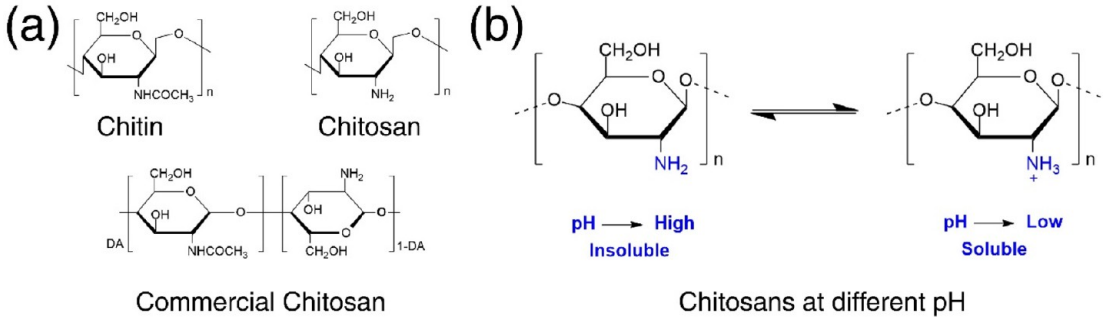

Figure 5. (a) Structures of chitin, chitosan, and commercial chitosan. (b) Structure of chitosan at different pH.[153,154]

semicrystalline polysaccharide is formed through β-(1 → 4) glycosidic bonding between glucosamine and the *N*-acetyl glucosamine units in chitosan.[155] Chemically, chitin and chitosan have different fractions of monomeric units. In chitin, the *N*-acetyl glucosamine groups are >50%, and the degree of acetylation (DA) refers to the number of acetamido groups. Chitosan has >50% glucosamine units, and the degree of deacetylation (DDA) is the number of glucosamine units. The DA and DDA are related as DA = 1 − DDA.[156,157] Figure 5a shows the chemical structure of chitin and chitosan.

Properties of Chitosan. The following properties of the chitosan makes it a versatile source for various applications.[153,158,159]

Solubility at Different pHs. Chitosan belongs to the family of amino polysaccharides. Its solubility is mainly controlled by the presence of amino groups (Figure 5b). At low pH, the protonation of amino groups makes the overall structure as a polycationic species. Below pH 6.0, chitosan acts as a strong base with a pK_a = 6.3. The active amino groups with cationic character help in attaching new groups under mild reaction conditions and also make it water-soluble. At higher pH (>6), its cationic character is transformed to anionic via deprotonation of amino groups, and chitosan becomes insoluble. Thus, the pK_a value of chitosan is used to tune its solubility and hence the degree of *N*-acetylation. The other advantages of chitosan are improved paste fluidity, anticoagulant behavior, and a high water-reducing ratio.

Different Molecular Weights (M_w). The molecular weight (M_w) can be easily tuned with the degree of acetylation. For example, a change in the degree of acetylation from 30 to 95% causes variation in M_w from 300 to over 1000 kDa, respectively.

Hydrogen Bonding. The different functional groups in the polymeric chain help in forming intermolecular hydrogen bonds. This particularly helps in providing hydrophilicity to the chitosan molecules and making them vulnerable to hydrolyzation and hence degradation. This also tailors the swelling property via absorbing water and makes them act as plasticizers.[160]

Biological Properties. The antimicrobial activity, bioadhesivity, biodegradability, adsorbable capability, bioactivity, hypolipidemic activity, and nontoxic nature makes chitosan interesting.[161−166] Among these different properties, the aspects of the antimicrobial activity of chitosan are discussed in detail, owing to the focus of the present review.

Antimicrobial Activity. Although the exact mechanism is not known, there are various proposed mechanisms in the literature. The polycationic character of chitosan present in fungi, viruses, and bacteria (Gram-positive and Gram-negative) is responsible for their intrinsic antimicrobial activity. In general, when polycationic chitosan electrostatically interacts with anionic cell wall components such as lipopolysaccharides and proteins of the microbial surface, the changes in the permeability barrier results into the leakage of intracellular components such as lactate dehydrogenase, nucleic acid, and glucose followed by the gradual shrinkage of the cell membrane. Furthermore, it prevents the uptake of nutrients inside the cell, attaches to DNA, and inhibits the synthesis of RNA and protein, which results in microorganism death.[159,163,167−170]

Researchers have used chitosan in different ways for antimicrobial activity. An important point worth mentioning is that the antimicrobial activity is feasible only in an acidic medium. At higher pH (>6.5), chitosan is usually insoluble. Thus, chitosan derivatives having solubility in the both acidic and basic medium are good candidates for antimicrobial activities. The ideal antimicrobial surface prevents adhesion and growth and has the potential to kill the microbes as well.[171]

The following section briefly outlines various chitosan-based antimicrobial applications. Although chitosan is mainly used in antimicrobial activity, the other applications of modified chitosan are bone regeneration, drug delivery, gene carrier, hemocompatibility, nanocarrier, and endothelial progenitor cell platform.[172] Researchers have used different ways to use chitosan for antimicrobial activity. Table 1 summarizes the antimicrobial properties of different chitosan-based surfaces.

El-Sayed et al. prepared chitosan/guar gum/*Roselle calyx* extract/zinc oxide (CS/GG/RE-ZnO) bio-nanocomposites and studied the antimicrobial activity on Ras cheese substrate for food packaging applications. Different Re-ZnO contents of 1, 3, and 5 wt % was added to CS/CG blends. The results showed that 3 wt % Re-ZnO exhibited the best performance against bacterial and fungal species especially *E. coli*, *Listeria monoytogenes*, and *Aspergillus terries*, which was attributed to the combined antibacterial properties of RE and ZnO extract. Also, Re-ZnO helps in forming a barrier against water vapor permeability.[173] Abouhussein et al. explored different cetylpyridinium chloride (CPC)-chitosan-based blends comprising of methylcellulose (MC), hydroxyethylcellulose (HEC), hydroxypropyl methylcellulose (HPMC) or poly(vinyl alcohol) (PVA) for the treatment of buccal mucosa for oral-based diseases.[174] Similar to that of chitosan, cetylpyridinium chloride drug is also cationic and has antimicrobial activity against Gram-positive bacteria, e.g., *S. mutans*, at lower concentrations and against Gram-negative bacteria at higher concentration.[175] Here, the polycationic nature of chitosan results in strong electrostatic interaction and attaches to the

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Table 1. Antimicrobial Properties of Chitosan and Chitosan-Based Surfaces[a]

material			best nanomaterials				
control surface	variant[b]	method (s)	contact angle (deg)	rms roughness (nm)	best suited for microorganism	antimicrobial activity/percentage/inhibition zone (mm)	ref
CS/guar gum/*Roselle calyx* extract	zinc oxide	NA	NA	NA	bacterial and fungal species	NA	173
CS	PVA* or HEC* or HPMC or MC	NA	NA	NA	*S. mutans*	NA	174
PVA/GA/CS	BPEO* or GEO	NA	NA	NA	*B. cereus, S. aureus, E. coli, S. typhimurium*	NA	183
CS/PPE	MOE	NA	NA	NA	*B. cereus*	NA	186
wool/CS	Ag* or Cu or Zn	NA	NA	NA	*S. aureus, E. coli*	~100%	204
BC	ChI or ChM	NA	NA	NA	*S. aureus* > *P. aeruginosa* > *C. albicans*		188
CS/PVA	LAE	NA	NA	NA	*C. jejuni*	2 (LRV)	189
Nylon-6 core	CS shell	NA	NA	NA	*S. aureus, P. aeruginosa*	NA	190
CS	CA or PC	NA	NA	NA	*P. aeruginosa, S. aureus*	NA	171
corn starch/CS	turmeric	NA	NA	NA	*S. aureus*	NA	195
PVA	chitosan/PHMG*	Kirby–Bauer (disk diffusion) method, and dilution and pour plate culture method	γ_s (mJ m^{-2}): PVA = 39.10 ± 1.12, PVA/CS = 37.07 ± 0.32, PVA/PHMG = 41.05 ± 0.35	10.6 ± 2.4	*S. aureus, E. coli*	≥5.6 (*S. aureus*), ≥6.0 (*E. coli*)	180
ammonium chitosans (CS612)/sodium alginate (SA)	multilayer structure (5.5 bilayers)	colony forming unit (CFU) determination and MTT assay	pristine PMMA: 100.56 ± 3.37 5.5 bilayers: ~65	257	*C. albicans*	99.82 ± 0.17%	193
CS (core)	OEO (shell)	NA	NA	NA	*A. alternata*	0.005% (MIC)	198
CS/PCL	OEO	colony counting method	112.07 ± 2.11	2.89 ± 4.67 nm	*S. aureus, L. monocytogenes, S. enteritidis, E. coli*	52.72 ± 1.01% (*S. aureus*), 41.06 ± 3.12% (*L. monocytogenes*), 49.37 ± 1.78% (*S. enteritidis*), 40.47 ± 3.36% (*E. coli*)	201
CS–gelatin	essential oils (cinnamon, pink clove, nutmeg, citronella, and thyme)	disk diffusion assay	NA	NA	*C. jejuni, E. coli, L. monocytogenes, S. typhimurium*	11.33 ± 0.94 mm	182
CS	capsaicin blends	disc diffusion test	91.02° ± 1.84	NA	*E. aerogenes*	15.44 ± 0.31 nm	202
CS	vanillin	disc diffusion test	NA	8.58	*E. coli, S. aureus*	log CFU = 4 mL^{-1}	203

[a]Compound abbreviations: BC–ChI: bacterial cellulose–chitosan nanocomposite by immersion, BC–ChM: bacterial cellulose–chitosan nanocomposite by impregnation in mass, CS: chitosan, PVA: poly(vinyl alcohol), LAE: ethyl lauroyl arginate, PEO: poly(ethylene oxide), 5CLO8Q: 5-chloro-8-quinolinol, PHMB: poly(hexamethylene biguanide) hydrochloride, CA: iota-carrageenan, PC: pectin, PHMG: poly(hexamethylene guanidine), PCL: poly(ε-caprolactone). Parameters: R_q: root-mean-square, γ_s: surface free energy, LRV: log reduction values, OEO: *Origanum vulgare* essential oil, MIC: minimum inhibition concentration [b]Species with the best antimicrobial performance are denoted by a *. In the case of no symbol being used for two or more species, then all the species in the cell show the best performance.

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negatively charged mucosal surface and is responsible for mucoadhesion. The −OH and $-NH_2$ groups of chitosan promote hydrogen bonding.[176,177] The results showed that the blends with PVA and HEC have more adhesion than that of the other blends due to more extensive hydrogen bonding.

In chitosan-based composites, usually an environmentally friendly polymer such as PVA is also used as an additive to improve the interfacial strength and mechanical properties including tensile strength, elongation, and flexibility.[49,178,179] The most important properties of PVA is hydrophilicity due to the enormous hydroxyl groups in the main chain along with biocompatibility, biodegradability, good chemical resistance, high crystallinity, and film-forming properties makes it a suitable candidate to use as an additive for biological applications.[180,181]

Essential oils are a complex mixture of low molecular weight compounds extracted from nature and plants and are generally used as food additives because of their advantage of inherent antimicrobial activity. This property is due to the different functional groups such as mono- and sesquiterpenes and phenolic compounds which interact with bacterial membrane components such as polysaccharides, fatty acids, and phospholipids. Various researchers have used essential oil derivatives for antimicrobial applications.[182]

The antimicrobial activity of PVA, gum arabic (GA), and CS-based biocomposites with the addition of black pepper essential oil (BPEO) or ginger essential oil (GEO) was tested on four different bacterial species (*E. coli*, *Salmonella typhimurium*, *Bacillus cereus*, *S. aureus*) by Amalraj et al.[183] Although the PVA/GA/CS composite film exhibits good intermolecular interaction, the purpose of the essential oils is to tailor the surface properties, along with increased flexibility which is due to the interruption of the polymeric network in the film. However, the drawback is the reduced tensile strength.[184,185] The PVA/GA/CS composite film is a compatible system with a compact and smooth microstructure along with few cavities on the surface. The addition of BPEO to PVA/GA/CS increased the roughness and the number of cavities with BPEO trapped inside them. The advantage is that the hydrophobicity of BPEO did not induce cracks in the system and make the overall microstructure more compatible. However, GEO leads to a rougher, coarser, and irregular surface, which is attributed to the migration of oil toward the film surface followed by its volatilization and evaporation of water. Furthermore, the BPEO-PVA/GA/CS composites exhibited excellent inhibition zones (16.82 ± 1.27−20.43 ± 2.04 mm) compared to those of GEO-PVA/GA/CS (14.59 ± 1.14−17.83 ± 1.77 mm) and PVA/GA/CS (4.14 ± 1.20−6.32 ± 1.23 mm). This is due to the continuous availability of the essential oils via sustained release on the surface and attack of the cytoplasmic membrane.

In another study, Olewnik-Kruszkowska varied the poly(hexamethylene guanidine) (PHMG) content in PVA−chitosan and PVA polymeric films.[180] The surface energies of the film decreased with the addition of chitosan in PVA. While PVA has a surface energy of 39.10 ± 1.12 mJ m^{-2}, it decreased to 37.07 ± 0.32 mJ m^{-2} with the presence of chitosan which is due to the diversion of the polar groups of the chain inside of the film. However, the PHMG attachment further increases the surface energy to 41.05 ± 0.35 and 38.90 ± 0.21 mJ m^{-2} for PVA−PHMG-1 wt % and PVA−chitosan−PHMG-1 wt %, respectively, suggesting that PHMG adds hydrophilicity in the modified composites. The antimicrobial properties were tested by two methods, viz., the Kirby−Bauer (disk diffusion) method and the dilution and pour plate culture method. PVA−PHMG exhibited the best antimicrobial activity, while PVA−chitosan−PHMG showed lower activity, due to the formation of a dense network between PVA and chitosan which blocks PHMG movement toward the outer layers. Thus, the antimicrobial activity was optimal for PVA−PHMG (*S. aureus* ≥ 5.6; *E. coli* ≥ 6.0) and reduced in the case of PVA−chitosan−PHMG (*S. aureus* ≥ 2.0; *E. coli* ≥ 1.6).

Pirsa et al. prepared an antibacterial/biodegradable film consisting of CS/pomegranate peel extract (PPE) and *Melissa officinalis* essential oil (MOE) and studied the detection of cream cheese spoilage.[186] Both MOE and PPE exhibit antimicrobial activities. The antioxidant and antimicrobial activity in PPE is due to the presence of flavonoids, azelaic acid, anthocyanidins, flavonones, anthocyanins, and aesthetic flavones. The surface properties were studied using the response surface method (RSM). The moisture content decreases with PPE addition, due to the hydrophobic nature of the PPE and bond formation with the chitosan hydroxyl groups thereby limiting water availability. In contrast, the 0.3−0.5% *w*/*v* content of MOE caused an increase in moisture content due to the increase in oil content in the composite. The thickness increases with the amount of uniform and homogeneous distribution of MOE and PPE at higher contents. The water vapor permeability increases with MOE content due to the formation of a porous network with cavities on the film. Also, the pure chitosan films are homogeneous and intact, while the PPE0.03%/MOE0.5% film has irregularities associated with cavities created by MOE and surface compression reduced by the essential oil. Furthermore, the antimicrobial study was carried out on three different composites, namely, pure CS film, CS/PPE0.03%/MOE0.0%, and CS/PPE0.03%/MOE0.5% on *E. coli* and *B. cereus*. The higher antimicrobial activity of CS/PPE0.03%/MOE0.5% is due to the presence of a large number of phenolic groups, viz., monoterpenes, glycosides, and flavonoids, and was more active for *B. cereus* than *E. coli*.

Sadeghi-Kiakhani loaded chitosan derivatives of Ag, Zn, and Cu NPs on wool yarn and studied the antimicrobial performance on *S. aureus* and *E. coli*. The antimicrobial activity arises from the electrostatic interaction between the positively and negatively charged amino groups and cell membranes, respectively, so the as-synthesized composites restrict the nutrient uptake and growth of the cells. The combined effect of metal NPs and chitosan induces the antimicrobial activity.[187] It was found that chitosan-Ag exhibited best antimicrobial performance of ∼100% for *E. coli* and *S. aureus*, respectively, and retained ∼95.60 and 92.57% performance after 10 washing cycles.

Cabañas-Romero et al. have compared the microbial activities of two different chitosan-based nanocomposites, namely, BC−ChI (bacterial cellulose (BC) paper sheets immersed in chitosan solution) and BC−ChM (BC pulp and chitosan were mixed followed by paper sheets production).[188] BC is an interweaved nanofiber network and randomly distributed. Chitosan was a uniformly distributed, homogeneous surface that had improved bonding between chitosan and BC and smaller pores in BC−ChI than that of BC−ChM. The antimicrobial activity of BC−Ch was tested on the bacteria *S. aureus* and *P. aeruginosa* and the yeast *Candida albicans*. Chitosan's sensitivity against different microbes follows the order: *S. aureus* > *P. aeruginosa* > *C. albicans*.

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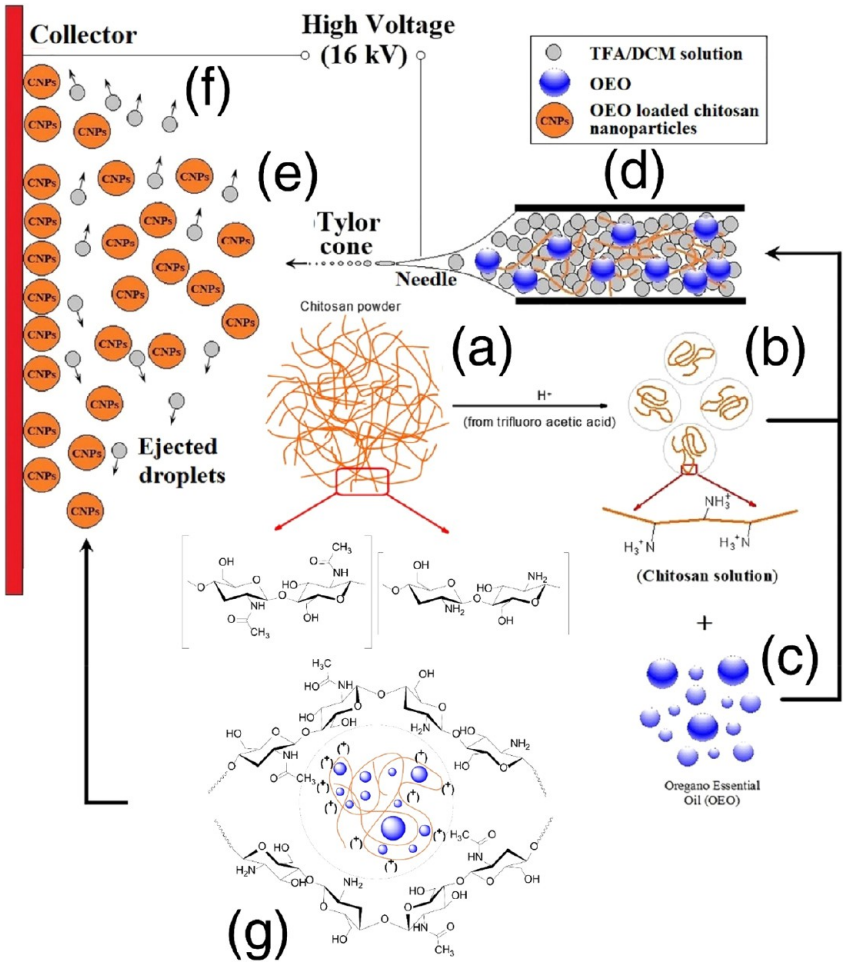

Figure 6. Electrospraying deposition process. (a) Chitosan powder. (b) Chitosan solution. (c) OEO addition. (d) Chitosan/OEO solution feeding in a syringe. (e) Taylor cone formation. (f) TFA/DCM solvent vaporization. (g) OEO-loaded CNPs fabrication. Reproduced with permission from ref 198. Copyright 2019 Elsevier.

Furthermore, BC−ChM has a greater inhibitory rate (83, 75 and 38% for *S. aureus*, *P. aeruginosa*, and *C. albicans*) and better prevented microbial growth compared to BC−ChI (65, 55, and 88% for *S. aureus*, *P. aeruginosa*, and *C. albicans*) because of the less compact surface of BC−ChM and its greater contact surface area. However, the antimicrobial effectiveness is similar for both types of composites and helps in inhibiting the microbial growth and biocidal activity.

Pulvirenti and co-workers studied the role of ethyl lauroyl arginate (LAE) (1−10% w/v) in CS-PVA blend films on microbial inhibition on the four major food bacterial pathogens including *E. coli*, *Campylobacter jejuni*, *Listeria monocytogenes*, and *S. typhimurium*.[189] The AFM showed that LAE addition adversely affected the film roughness. Starting with a pure CS and PVA blend, the film is relatively homogeneous without the presence of pores or cavities. The film roughness abruptly increased in 5 and 10% LAE, showing the strong interaction between LAE and CS-PVA blends. Furthermore, the antimicrobial activity was analyzed by disk diffusion assay. The LAE is usually more effective against *C. jejuni*, resulting in the halo size becoming 3- to 5-fold wider. However, the results of 5 and 10% LAE were similar for all the bacteria. Furthermore, the antimicrobial activity was also evaluated in a liquid medium which increases with the increase in LAE content, and the maximum reduction value of 2 was obtained at 10% LAE-CS-PVA for *C. jejuni*.

Haghighi et al. comprehensively studied and compared the antimicrobial performance of five different essential oils including cinnamon, pink clove, nutmeg, citronella, and thyme essential oils in chitosan−gelatin blend films.[182] Gelatin is a hydrophilic protein with good compatibility and affinity for chitosan to form a blend. Furthermore, the oil droplets remain embedded on the surface of the films on drying. However, cinnamon and nutmeg films show pores on their surfaces which is associated with the fast drying of oils due to their high volatility. The control chitosan−gelatin film did not show any antimicrobial activity. This is due to the unavailability of chitosan caused by the lack of diffusion, while gelatin did now show this behavior. However, different essential oils show antimicrobial behavior. It can be seen that thyme essential oil is most effective for the antimicrobial performance of 31.67 ± 1.71%, which is due to it having the highest water solubility, compared to that of 23.61 ± 0.58% for the control chitosan−gelatin surface and the range of 20.36 ± 1.09% to 30.24 ± 0.75% for nutmeg and cinnamon based blends, respectively.

Keirouz et al. used Nylon-6/chitosan core/shell electrospun nanostructures for antimicrobial surfaces.[190] The advantage of using these core/shell nanofillers is the dual antimicrobial action governed by the polyamide-6/poly(hexamethylene

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biguanide) hydrochloride (PHMB) and 5-chloro-8-quinolinol (5CLO8Q) release from the Nylon-6 and chitosan shell, respectively. It was found that the core/shell type of morphology is most effective in decimating the growth of live bacteria.

Martins et al. fabricated layer-by-layer films using iota-carrageenan (CA) or pectin (PC) on chitosan, termed as polyelectrolyte multilayers (PEMs), to test the bactericidal activities against *P. aeruginosa* and *S. aureus*.[171] The number of layers with chitosan-terminated ends were between 5 and 15. The WCA of CA-chitosan was 25 ± 0.2° which was low compared to that of PC-chitosan having a value of 51 ± 0.2°. Thus, CA enhanced the wettability of the overall film. The improved wettability is also desired to develop antiadhesive surfaces for the microbes.[191] Both the surfaces showed bactericidal effects against *P. aeruginosa* and *S. aureus* at low pH (5.0).

López et al. prepared a chitosan and hyaluronic acid (HA) based thin polymer multilayer film on titanium substrates to release a β-amino acid based peptidomimetic of antimicrobial peptide.[192] The antimicrobial testing was carried out against *S. aureus* in 96-well plates given by the Clinical and Laboratory Standards Institute. It was found that the release of β-peptide continued for 28 days, while the film selectively inhibited the formation of *S. aureus in vitro* for nearly 24 days and retained the viability of MC3T3-E1 osteogenic mammalian cells. In a similar multilayered type coating, Jung et al. selected ammonium chitosans (CS612) as the positive and outermost layer and sodium alginate (SA) as the negative layer to use for a *C. albicans* fungal-repellent surface on a PMMA disc.[193] The advantage of using CS612 is its long alkyl chain thereby making it highly durable. However, the SA layer helped to reduce the contact angle to ∼60° (5.5 bilayers) as compared to 100.56 ± 3.37° (pristine PMMA). The roughness of 5.5 bilayers (257 nm) was lower than that of pristine PMMA disc (336 nm). While PMMA did not show antifungal properties, the multilayered CS612/SA killed 99.82 ± 0.17% of *Candida* in 4 h. However, if SA was replaced as the top layer, then the antifungal property is also observed but not as efficient as that of CS612. Furthermore, *in vitro* cytotoxicity test (ISO 10993−5 and 10993−12) showed that cell viability is not affected by varying temperatures. The MTT assay (direct contact method) indicated that pure PMMA has a low cell survival level, while CS612 on the top layer is most suited for a good cell proliferation rate as compared to SA on the top layer. This shows that positively charged CS612 has more cell adhesion tendency and lead to improved performance.[194]

Schaefer et al. used turmeric as an additive in cornstarch and chitosan based blends.[195] The curcumin found in the turmeric has a good wound healing property and excellent antimicrobial activity against bacteria.[196,197] However, it was observed that all chitosan-containing formulations such as chitosan, chitosan−starch, chitosan−turmeric, and chitosan−starch−turmeric show antimicrobial activity against *S. aureus*. Some authors also found that very low content of turmeric is not effective for antimicrobial activity because of its hydrophobic nature and is much less stable in an aqueous environment. However, the higher turmeric content can be further studied to investigate the behavior. Thus, the main ingredient was chitosan for antimicrobial activity. Cao et al. prepared easily penetrable CS encapsulated with poly(2-methacryloyloxyethyl phosphorylcholine) (CS-PMPC) nanocapsules for antimicrobials. Two different molar ratios of *N*-(3-aminopropyl) methacrylamid (APM)/MPC of 4:1 and 1:1 were also compared, named as P(MPC_1-*co*-APM_4)-CS and P(MPC_1-*co*-APM_1)-CS, respectively. The reason for replacing a few contents of PMC with APM was to improve the electrostatic attraction by increasing the positive charges on the surface.

Yilmaz et al. used the electrospraying method to design chitosan NPs (CNPs) loaded with *Origanum vulgare* L. essential oil (OEO) as shown in Figure 6.[198] The OEO/CH proportions were 0:1 (S_0), 0.0625:1 (S_1), 0.125:1 (S_2), 0.25:1 (S_3), and 0.5:1 (S_4) mL/g and the average size of the NPs was between 290 and 483 nm. The increase in OEO concentration adds more positive charges on the surface of the NPs as evident from zeta potential values which increase from +25.2 ± 3.13 (S_o) to +47.7 ± 1.05 (S_4) mV. The study was carried out to test against *Alternaria alternata*. The antimicrobial activity was tested by calculating the minimum inhibition concentration (MIC) which was smallest for S_4 having a value of 0.005%, compared to 0.02% for S_0. A higher OEO concentration disrupts the cell walls lipids and leads to transudation of the lipids and cell death.[199] Also, the terpenes can damage the mitochondrial membrane to kill the microbes.[200] Thus, OEO helps in antimicrobial activity.

In a similar study, CS, OEO, and poly(ε-caprolactone) (PCL) were electrospun to develop antimicrobial fibrous mats.[201] The average diameter was in the range of 332.4 ± 138.7 (CS/PCL) to 206.5 ± 96.90 (CS/OEO(5%)/PCL). The advantage of adding OEO is the smooth surface because the liquid state of the oil decreases the viscosity of the electrospinning solution. It is also clear from the decrease in roughness from 84.56 ± 3.75 nm to 62.89 ± 4.67 nm for CS/PCL and CS/OEO(5%)/PCL, respectively. However, the wettability was not affected significantly by varying the OEO concentration and slightly decreases from the control surface (117.65 ± 0.35°) to 112.07 ± 2.11° for 5% OEO content. The antimicrobial test was carried out via the colony counting method after 3 and 6 h. The results indicate that the antimicrobial efficiency after 6 h was not efficient owing to the high reproductivity of bacteria and that the inhibition efficiency decreased with time. So, CS/OEO/PCL is not much more efficient than the NPs discussed earlier.

In another study, chitosan with three different concentrations of capsaicin blend was used to test against various Gram-positive and Gram-negative bacteria.[202] The anti-inflammatory, antioxidative, anticancer, antiobesity, and analgesic properties of capsaicin make it a likely candidate for antimicrobial activity. Three different concentrations of capsaicin, viz., 0.3, 0.6, and 1.2 mg, and 200 mg of chitosan were used to prepare the blend and are abbreviated as CCF-0.3, CCF-0.6, and CCF-1.2, respectively. The contact angles show an increase in hydrophobicity with the addition of capsaicin, and the values were 81.11° ± 1.31 (chitosan), 85.08° ± 4.70 (CCF-0.3), 87.57° ± 2.46 (CCF-0.6), and 91.02° ± 1.84 (CCF-1.2), suggesting the hydrophobic nature of capsaicin and homogeneous mixture blends. The film surface becomes rough at a very high concentration of capsaicin (CCF-1.2), and below this concentration, the overall film was more homogeneous and smoother. Furthermore, the increase in capsaicin concentration to CCF-1.2 led to maximum antimicrobial performance and the maximum zone of inhibition as compared to those of CCF-0.3 and CCF-0.6. For example, the maximum inhibition zone of 13.19 ± 0.87 mm was obtained for *Proteus mirabilis* while CCF-0.3 and CCF-0.6 exhibited values of 4.85 ± 0.42 and 9.26 ± 0.68 mm,

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respectively. This is attributed to the interaction between capsaicin's phytochemicals and cell walls of bacteria causing lysis of the bacterial cell wall. The antimicrobial activity of the blended surface showed better performance against Gram-negative bacteria than against Gram-positive bacteria. The lipid−lipid interaction caused the disruption of the peptidoglycan structure in Gram-negative bacteria. With regard to Gram-negative bacteria, *Enterobacter aerogenes* was most sensitive, while *Proteus vulgaris* shows remarkable resistance against antimicrobial agents due to the ability to elongate themselves and secrete a polysaccharide on contact with the blend surface. In contrast, Gram-positive bacteria such as *S. aureus* and *S. mutans* show similar antimicrobial behavior, and the maximum resistance was exhibited by *Bacillus thuringiensis* because of endospores.

Buslovich et al. coated chitosan with vanillin, a volatile, naturally occurring antimicrobial agent, using a concentration of 3.7 μmol/g and ultrasonic irradiation.[203] The film roughness increased to 8.58 nm in chitosan−vanillin, while pristine chitosan exhibits a roughness of 5.73 nm. The effect of roughness also seen in the antimicrobial activity as studied by counting the CFU against two bacteria Gram-negative *E. coli* and Gram-positive *S. aureus* bacteria. However, the vanillin did not affect the antimicrobial performance, and the decrease from log CFU of 10 mL^{-1} in pure vanillin to ∼4 mL^{-1} was attributed to the presence of chitosan. The chitosan−vanillin blend was beneficial against the yeast and mold in preserving the food quality.

Biodegradable Antimicrobial Materials. Although various conventional chemical-based antimicrobial agents have been developed, there is a need to develop natural and biodegradable biocides with improved antimicrobial performance. The aim should also be to protect unwanted microorganisms and kill only the targeted pathogens. Thus, the present section deals with biodegradable-based antimicrobial agents.

Apart from synthetic polymers, biodegradable polymers have also been researched to harness antimicrobial activity. These materials can be regenerated by the enzymatic action on the microbes or living species. The advantage of natural and biodegradable-based products is their environmental friendliness.[205,206] The raw component is mainly biomass. Different biomass-based derived polymers such as proteins and polysaccharides and synthetic polymers like polylactic acid (PLA), PVA, ethylene−vinyl alcohol (EVOH) and polycaprolactones (PCL). The other examples are genetically modified bacterial cellulose or PHAs.[207−211] The researchers have explored different ways to utilize biodegradable polymers-based antimicrobial activity as mentioned below.

Romano et al. designed poly(ε-caprolactone) nanocapsule suspensions (NCs) containing OEO and *Thymus capitatus* (thyme) essential oils to act against *E. coli* and *Kokuria rhizophila*.[212] The thyme-based capsules show good potential in treating microbes having a MIC value of 0.3 mg mL^{-1} for both microorganisms while OEO-based antimicrobial agents show MICs of 0.6 and 0.5 mg mL^{-1} against *E. coli* and *K. rhizophila*, respectively. The reason for the high activity of thyme-based NCs is due to the high content of carvacrol (73%) which disrupts the cell membrane.

In another study, Musiol et al. have used biodegradable polymer nanocomposites for *S. aureus* degradation. Poly[(*R*)-3-hydroxybutyrate-*co*-4-hydroxybutyrate)] was used as a polymer matrix, while different contents of wood flour and nisin were used to provide biodegradation. The bacteriocin nisin was also incorporated in PLA and PLA/polyethylene glycol (PLA/PEG) blends to test *Micrococcus luteus* by Holcapkova et al.[213] The effect of temperature on the antimicrobial activity was also studied. The results showed that nisin/PLA retained antimicrobial activity up to 70%, while PEG adversely degraded the nisin above 120 °C.

Lignin, the second most abundant biopolymer after cellulose, is a renewable material and exhibits antimicrobial properties. In a work performed by Domínguez-Robles et al., the lignin was added with biocompatible/biodegradable poly(butylene succinate) (PBS) to form biocomposites against *S. aureus*.[214] The contact angles of the composites were similar to that of the pure PBS having a value of ∼75°. However, the biocomposites show ∼90% reduction in the adherence capacity concerning control PBS. Furthermore, İnal and Mülazımoğlu used different ratios of poly([2-(methacryloyloxy)ethyl] trimethylammonium chloride) (PMETAC) with gelatin nanofibers to act against *S. aureus*, *E. coli*, and *Acinetobacter baumannii*. The MIC with of gelatin nanofibers with 80 wt % PETAC was 109.15 ± 10.76 μg mL^{-1}, while it was 193.57 ± 20.59 μg mL^{-1} for *E. coli*.

Food additives such as pomegranate (*Punica granatum* L.) peel powder have also been incorporating in gelatin for improved antimicrobial performance.[215] The antimicrobial activity of pomegranate is associated with the presence of high levels of ellagitannins.[216] The sensitivity of the tested microbes of 5% (w/w based on gelatin weight) follows the order: *S. aureus* (7.00 ± 0.71 mm) > *L. monocytogenes* (5.13 ± 0.25 mm) > *E. coli* (4.13 ± 0.25 mm). In a similar study, passion fruit byproduct extracts were used to produce poly(DL-lactide-*co*-glycolide) (PLGA) with different ratios of different PLGA lactide to glycolide of 50:50 and 65:35. *E. coli* and *Listeria innocua* were tested, and the results showed that different ratios have different antimicrobial performance with seed and cake extracts. In summary, the PLGA 65:35 particles were effective against *L. innocua* and exhibited MIC values of 373 and 188 μg mL^{-1} for the seed and cake extracts, respectively.

Furthermore, the biodegradable guanidinium-functionalized polycarbonates were designed for *in vivo* antimicrobial activity against *A. baumannii*, *E. coli*, *Klebsiella pneumoniae*, *S. aureus*, and *P. aeruginosa*.[217] At the optimum degree of polymerization (DP) = 20, different hydrophobic spacer groups such as alkyl (ethyl, propyl, butyl, and pentyl) and aromatic (cyclohexyl, phenyl, and benzyl) groups were examined and the improved hydrophobicity of the spacer groups from alkyl to aromatic results in an increase in the hemolysis.

Hassan et al. fabricated the cellulose nanowhiskers Ag NPs (CCNWs-AgNPs) with nanocomposited chitosan and carboxymethyl cellulose (CMC) using a freeze-drying method for bone tissue engineering applications. Different types of characterization studies have been explored to prove the enhanced scaffold porosity, mechanical strength, and swelling properties with enhanced resistance on enzymatic degradation and toxicity analysis of the as-prepared scaffolds. The excellent antimicrobial activity and improved cell growth was witnessed for the CCNWs-AgNPs incorporated CMC scaffolds, which gained significant attention for bone tissue engineering applications.[211]

A BC biocomposite gel-film with *Bacillus subtilis* cells was tested for biomedical applications. A high antagonistic activity was evidenced for the *B. subtilis* (BS) immobilized cells against

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Table 2. Antimicrobial Properties of Biodegradable Polymer-Based Surfaces

material							
control surface	variant[a]	method (s)	contact angle (deg)	rms roughness (nm)	best suited for microorganism	antimicrobial activity/ percentage/inhibition zone (mm)	ref
marble	NCs containing *O. vulgare* and *T. capitatus* EOs	agar discs contact test	NA	NA	*E. coli*, *K. rhizophila*	0.3 mg mL^{-1}	212
P(3HB-*co*-4HB)	P(3HB-*co*-4HB)/WF/nisin	disc diffusion assay	NA	NA	*S. aureus*	3.5 ± 1 mm	222
PBS	lignin	agar discs contact test	∼75	NA	*S. aureus*	90% reduction	214
gelatin	PMETAC	broth microdilution procedure	NA	NA	*S. aureus*	109.15 ± 10.76 μg mL^{-1}	223
gelatin	pomegranate (*Punica granatum* L.) peel powder	disk diffusion method	NA	NA	*S. aureus*	7.00 ± 0.71 mm	215
PLA and PLA/ PEG blends	nisin	agar diffusion method	NA	NA	*M. luteus*	∼100% (PLA/nisin)	213
polycarbonates	guanidinium	agar diffusion method	NA	NA	*S. aureus*	3.9 μg mL^{-1}	217
free extract	PLGA 50:50 and 65:35 particles	microdilution method	NA	NA	*L. innocua*	188 μg mL^{-1}	224

[a]NCs: nanocapsules suspensions, EOs: essential oils, PBS: poly(butylene succinate), PMETAC: poly([2-(methacryloyloxy)ethyl] trimethylammonium chloride, PLA: polylactic acid, PEG: polyethylene glycol, PLGA: poly(DL-lactide-*co*-glycolide)

causative agents responsible for wound infections such as *S. aureus, Staphylococcus epidermidis*, *E. coli*, and *P. aeruginosa*. On the basis of the mechanisms explored, this work claims that the BC/BS biomaterial would be a universal wound coating as well as a sanitary hygienic product. Also, it was reported that the antibacterial activity was enhanced mainly due to the lytic enzymes action actively lysing cells of bacteria (Gram-positive and Gram-negative).[218]

State-of-the-art progress in cellulose-based hydrogels for advanced biomedical applications was presented by Fu et al. The topics covered in the review were synthesis methods, characterization methods based on physicochemical and mechanical properties, and emerging biomedical applications of cellulose-based hydrogels such as tissue engineering, drug delivery, bioimaging, wound dressing, and wearable sensors. The current challenges and future prospects on the biomedical applications of cellulose-based hydrogels were discussed at length. It was concluded that other than biomedical applications there are few more emerging fields which can utilize the great potential of cellulose hydrogels, particularly in agriculture and chemical fertilizers applications.[219]

One of the reviews on cellulose based superhydrophobic coatings was summarized 40 different approaches adopted to fabricate superhydrophobic coating. Detailed attention was paid to explaining the antiwetting properties of cellulose-based coatings along with the other functional properties such as transparency, gas permeability, anti-bio-fouling, self-healing properties, UV shielding, packaging, and photoactivity. The range of applications of cellulose, including self-cleaning and breathable clothing, water and stain repellence, filters for oil/ water separation, cost-effective and biodegradable lab-on-a-chip devices, have gained considerable attention in the real world as the products are made from renewable sources with minimal material consumption.[220] The nanocellulose-based antimicrobial materials applications such as drug carriers, wound dressings, and packaging materials were reviewed extensively by Li et al.[39] The challenges of industrial production of nanocellulose-based antimicrobial materials were also discussed. The promising future of BC was reviewed based on wound dressing applications by Portela et al.[221] This review summarized the physicochemical properties, mechanical properties, cell adhesion, biocompatibility, and nontoxicity properties of BC in tissue engineering applications, especially for wound-healing applications. It was concluded that BC can be a great alternate biopolymer to petroleum-based ones as it shows excellent biocompatibility, flexibility for molding while being used for 3D bioprinting, nontoxicity, native purity, environmental friendliness, and recyclability.

Thus, biodegradable polymers are also becoming an attractive alternative for antimicrobial performance owing to their low cost, renewability, and environmental friendliness. Table 2 compares different biodegradable-based antimicrobial agents.

Protein-Based Antimicrobial Surfaces. Proteins are the building blocks of biological structures and tissues and regulate physiological processes and somatic functions.[225] Peptides offer several advantages such as biocompatibility, nontoxicity, self-assembly and ecofriendliness, and recently "peptoids" have been reported with excellent antimicrobial properties.[226−228] In the last 50 years, the advancements in antibiotic drugs were also accompanied by an increase in the cases of antimicrobial resistance. Thus, there is a constant need for new antibiotics including AMPs-based antibiotics which are also a part of multicellular organisms. More than 750 AMPs have been discovered in different living animals, plants, fungi, bacteria, and viruses.[229,230]

Brogden has classified AMPs into five subgroups based on the amino acid composition and structure as follows:[231]

(i) anionic peptides
- small peptides having molecular weights in the range of 721.6−823.8 Da
- responsive to both Gram-positive and Gram-negative bacteria
- active in the presence of zinc cofactor
- examples: Maximin H5, dermcidin, glutamic and aspartic acids

(ii) linear cationic α-helical peptides
- contain ∼290 cationic peptides

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Table 3. Antimicrobial Properties of Protein-Based Surfaces[a]

material							
control surface	variant	method (s)	contact angle (deg)	rms roughness (nm)	best suited for microorganism	antimicrobial activity/percentage/ inhibition zone (mm)	ref
stainless steel	Dopa-conjugated peptide amphiphile and REDV-conjugated peptide amphiphile	counting the number of live cells using fluorescence microscope images	<10	168.5 ± 16.1	HUVEC, A7r5 and A10 cells	70% viability for A7r5	239
PDMS	HEG/tripeptide (Arg−Gly−Asp)/cell-adhesive peptide	counting the number of live cells using fluorescence microscope images	NA	NA	*S. aureus*	$5.15 \pm 1.21 \times 10^3$	243
PMOXA and PDMS polymeric micelle	KYE28	static biofilm formation assay	78	NA	*E. coli*	∼80 (CFU)	244
GG8	FF8	MTT assay	NA	NA	*E. coli*	∼100%	242
natural hairpin AMP PG-1	cCF10	microtiter dilution method	NA	NA	*E. faecalis*	4 μM	245
LK13 peptide and tobramycin	CS-PEG-LK_{13}	agar plate counting method	NA	NA	*P. aeruginosa*	8 $\mu g\ mL^{-1}$	247
polymyxin	darobactin	micro broth dilution	NA	NA	*E. coli*, *K. pneumoniae*	2 $\mu g\ mL^{-1}$	246
colistin	ZY4	tube microdilution assay	NA	NA	*P. aeruginosa*, *A. baumannii*	*P. aeruginosa* (2.0−4.5 μg/mL) and *A. baumannii* (4.6−9.4 μg/mL)	248
Ce6-SiNPs	GP-Ce6-SiNPs	agar plate experiments	NA	NA	∼98 and ∼96% against *S. aureus* and *P. aeruginosa*	∼98% *S. aureus*	249
PVA-*co*-PE	BDCA-RNM	agar plate counting method	NA	NA	*E. coli*	>99.9999%	250

[a]HUVEC: human umbilical vein endothelial cells, A7r5: rat aortic smooth muscle cells, A10: rat aortic smooth muscle cells, PMOXA: poly(2-methyl-2-oxazoline), PDMS: poly(dimethylsiloxane), KYE28: (KYEITTIHNLFRKLTHRLFRRNFGYTLR), GG8: KRRGGRRK, FF8: KRRFFRRK, CS-PEG-LK_{13}: chitosan−polyethene glycol-peptide conjugate, ZY4: VCKRWKKWKRKWKKWCV-NH_2, GP: glucose polymer, Ce6: chlorin e6, SiNPs: silicon NPs,

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- relatively short repeating units of amino acids (<40), associated with a kink in the middle and lack cysteine residues
- disordered in aqueous solution and partially or completely convert to α-helix in the presence of phospholipid vesicles, trifluoroethanol, sodium dodecyl sulfate (SDS), micelles and liposomes
- examples: cecropins, magainin, pleurocidin, seminalplasmin

(iii) cationic peptides enriched for specific amino acids
- contain ∼44 cationic peptides
- lack of cysteine residues and are linear and sometimes form extended coils
- rich in certain amino acids such as prophenin (proline: 57% and phenylalanine:19%) and indolicidin (tryptophan residues)
- examples: proline, arginine, glycine, tryptophan, histidine

(iv) anionic and cationic peptides that contain cysteine and form disulfide bonds
- comprised of ∼380 members
- examples: peptides containing 1−3 disulfide bonds (brevinins, protegrin, and α-, β-, or θ-defensins) as well as drosomycin

(v) anionic and cationic peptide fragments of larger proteins
- also exhibit antimicrobial activity
- examples: lactoferricin, casocidin I

The antimicrobial activities of peptides depend on their structure such as size, sequence, conformation, charge, hydrophobicity, and amphipathicity. Although peptide-mediated antimicrobial activity can be very rapid, such that it cannot be characterized by various available techniques or can happen in 15−90 min, the exact mechanism is still not clear. However, the specific steps of the overall process can be summarized by three proposed mechanisms as follows.[231−234]

Barrel-Stave Model. This model is named based on the resultant "barrel and stave" type structure obtained upon the interaction between peptides and cell membrane. The peptide helices arrange in the form of the bundle, and the central lumen structure is similar to a barrel with helical peptides forming a stave-type architecture. The alamethicin response with a membrane follows this model. The hydrophobic and hydrophilic regions of the helical peptides align with the lipid region of the bilayer and interior region of the pores, respectively.

Carpet Model. In this model, the peptides accumulate and are arranged parallel or in-plane to the surface of the membrane in a carpetlike manner. The electrostatic interaction between peptides and membranes is responsible for this arrangement. After the threshold concentration, the formation of transient toroidal holes takes place which allows the passage for upcoming peptides into the membrane. At high peptide concentration, the peptides disrupt the bilayer and form micelles. Ovispirin shows this type of antimicrobial activity.

Toroidal-Pore Model. In this model, the antimicrobial peptide helices form a toroidal-pore-type of morphology by insertion and bending the lipid monolayers. The structure extends leaflets of the membrane from top to bottom in a continuous manner. The polar groups of peptide and lipids associate each other during the toroidal pore formation. Various peptides such as magainins, protegrins, and melittin exhibit this type of activity.

Peptides have also been explored as antifouling coatings to minimize the nonspecific adsorption of microbes. Sakala and Reches have classified peptides into different parts and thoroughly discussed their significance for the antimicrobial activity.[235] The main classifications include self-assembled peptides, PEGylated peptides, zwitterionic peptide-based self-assembled monolayers, peptidomimetic coatings, and AMPs grafted on surfaces. The most used peptides are self-assembled. The advantage of these peptides is the formation of a well-ordered structure from simple building blocks, dipeptides, or amino acids, consisting of 10−50 amino acids.[236] The self-assembled supramolecular structures are associated with the various types of noncovalent interactions including electrostatic force, hydrogen bonding, hydrophobic interaction, and $\pi-\pi$ stacking interaction.[237,238] The various aspects and applications of proteins based antimicrobial performance are detailed below and summarized in Table 3.

Ceylan et al. investigated the fabrication and application in antifouling surfaces using dopamine and REDV providing adhesion to the surface and selective growth of endothelial cells on the stainless-steel surface.[239] The two phenylalanine residues modified with fluorine directed self-assembling and form $\pi-\pi$ stacking. The improved hydrophobicity prevents the adhesion of bacteria. Furthermore, the cell viability was also measured for three cell lines, namely, human umbilical vein endothelial cells (HUVEC), A7r5 rat aortic smooth muscle cells, and A10 rat aortic smooth muscle cells. HUVEC showed maximum relative cell adhesion of ∼8 than that of stainless steel having a value of 1. However, A7r5 and A10 cells exhibited similar relative cell adhesion of ∼1. The A7r5 and A10 cell viability showed maximum decrease to ∼70%, while it remains similar for HUVEC (∼100%).

The self-assembling peptide-based hydrogels also attract sufficient attention,[240] and Schnaider et al. showed potent application by selecting organic (nanofibrillar silk microgels)/inorganic (Ag) hybrids toward antimicrobial activity both *in vivo* and *in vitro* against *E. coli*.[241] The mechanism follows the two-step form of bacterial adherence and consequent eradication. The 75% of the bacteria were eliminated using the specifically designed hydrogels.

In another work, Zhang and co-workers developed a novel cationic octapeptide, termed FF8 or KRRFFRRK, which is constituted of arginine, lysine, and phenylalanine.[242] It undergoes self-assembly at a higher pH (>9.4) into amyloid-like fibers. Thus, it acts by self-assembling into nanofibers upon the contact with negatively charged lipid membrane, similar to the "carpet model". The antimicrobial activity of the resultant structure was tested with *E. coli* and *S. aureus*, and the results exhibit a stronger inhibitory effect for *E. coli*. The weaker inhibitory effect of *S. aureus* was associated with its thick cell walls which limited the interaction between FF8 and the cell membrane. Furthermore, the viability tests showed that *E. coli* was completely killed in 30 min, showing good antimicrobial activity.

In another study, Li et al. designed a trilayered architecture: a top layer, cell-adhesive peptide; middle layer, infectious-environment-responsive peptide; and bottom layer: antifouling hexaethylene glycol (HEG).[243] The bottom layer acts as a surface resistant to microbial adhesion and can bind to surfaces such as silicon, PDMS, and glass via silane chemistry. The reason for HEG's effectiveness is attributed to its repulsive elastic force to the upcoming macromolecules toward it due to compression. The middle layer interacts with two bacterial

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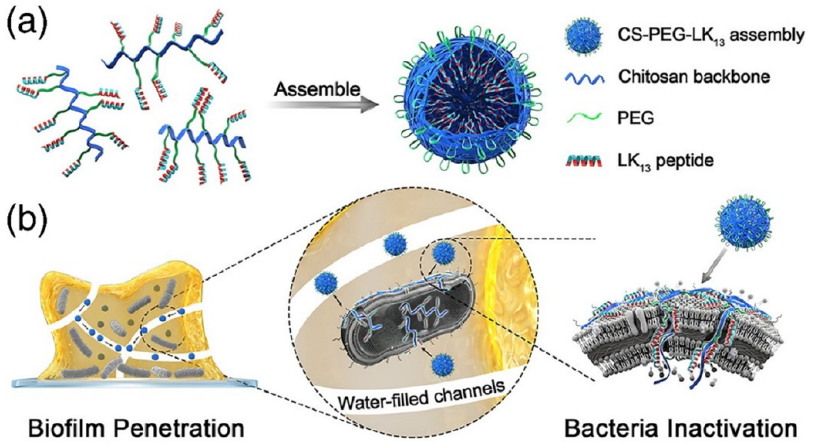

Figure 7. Schematics of (a) CS-PEG-LK13 self-assembly. (b) Antibacterial activity on the biofilm of the CS-PEG-LK13 assembly. Reproduced with permission from ref 247. Copyright 2020 American Chemical Society.

enzymes, namely, gelatinase (G) and coagulase (C). The top layer is a peptide Arg−Gly−Asp (RGD) that promotes cell adhesion. The antibiofilm activity showed that the surfaces incubated with positive bacteria are relatively clean and that biofilm formation takes place with Gram-negative bacterial strains. Thus, the HEG layer is more responsive for Gram-positive bacteria, leading to improved antimicrobial activity.

AMPs have gained much attention due to their efficient antimicrobial activities. The electrostatic interaction between the positively charged amino acid and negatively charged lipid bilayers leads to cell damage and killing of microbes.

Rigo et al. used an active and a passive approach with and without, respectively, attaching AMP KYE28 (KYEITTIH-NLFRKLTRLFRRNFYTLR) on a poly(2-methyl-2-oxazoline) (PMOXA) and poly(dimethylsiloxane) (PDMS) polymeric micelle.[244] KYE28 is found in human heparin cofactor II and shows bactericidal action against the cell membrane. The WCA also increased to 78° with KYE28 addition as compared to 63° for micelle-immobilized surfaces. The increased hydrophobicity was due to the amphiphilic nature of the peptide. The antimicrobial activity was checked by immersing different substrates in an *E. coli* inoculum (5×10^4 CFU mL^{-1}). The KYE28-based substrates successfully reduced the bacterial adhesion and were more efficient than micelle-immobilized surfaces. This also resulted in bacterial survival of only 16%, while micelle-based surfaces show 43% survival. Thus, the combined effects of active and passive defense mechanisms leads to improved antimicrobial performance.

Xu et al. constructed different AMPs targeted at *Enterococcus faecalis* with a targeting domain of enterococcal pheromone cCF10, and target specificity was improved by the optimized active center of the AMP.[245] The specially designed films were tested on Gram-positive bacteria (*S. aureus* 1005, *E. faecalis* 25922, and *S. epidermidis* 7913) and Gram-negative bacteria (*S. typhimurium* 29213, *S. pullorum* 43300, and *E. coli* 12228). Site-specificity was achieved by tuning the electrostatic interactions between the AMPs and microbes. A weaker interaction is supposed to prevent the entrance of molecules into the microbial membrane and made the antimicrobial inactive. The net charges on the peptides were tuned to +6 (cCF10-C6), +4 (cCF10-C4), and +3 (cCF10-C3). It was shown that bacterial growth is unaffected by cCF10. C6 and C6-cCF10 exhibited similar activity, and cCF10-C6 showed 4-fold higher bactericidal activity for *E. faecalis*. Thus, cCF10 provided selectivity for the antimicrobial activity against *E. faecalis*. Furthermore, cCF10-C4 lead to reduced activity toward all the untargeted bacteria except for *E. faecalis*. The further decrease in the charge of cCF10-C3 and random peptide severely affected the activity for all the bacteria. Thus, a suitable pheromone−receptor interaction helps in selectively acting on specific microbes.

In another interesting study, Imai et al. reported a new antibiotic, darobactin, to selectively kill *in vitro* and in animal infections associated with Gram-negative pathogens.[246] Darobactin is a heptapeptide having an amino acid sequence of $W^1-N^2-W^3-S^4-K^5-S^6-F^7$. The MIC value of 2 $\mu g\ mL^{-1}$ was obtained against *E. coli* and *K. pneumoniae*.

Apart from different bacteria, WHO also listed *P. aeruginosa* as a critical pathogen in 2017. The biofilms are 100−1000 times more tolerable toward antibiotics than that of bacteria associated with the surrounding extracellular polymeric substance (EPS). This helps in restricting the antibacterial agents from deep penetration in a biofilm. Furthermore, biofilms have two important characteristics, namely, water-filled channels for nutrient/waste transportation having sizes ranging up to micrometers and EPS which makes the biofilm highly charged and helps in adsorbing ionic constituents. The EPS is usually composed of polysaccharides, lipids, proteins, and extracellular DNA.

From the viewpoint of biofilm characteristics, Ju et al. prepared a CS−PEG−peptide conjugate (CS-PEG-LK13, where LK13 refers to the sequence LKLLKKLLKKLKK) to study antimicrobial activity against *P. aeruginosa* biofilms, and the mechanism is as shown in Figure 7.[247] In Figure 7a, in an aqueous environment CS-PEGLK13 self-assembled into neutrally charged nanospheres of size 100 nm with LK_{13} and PEG in the core and on the surface, respectively, and was capable of traveling in a water-filled channel. However, it disassembles upon contact with the bacterial membrane, and the exposed cationic and hydrophobic domains of α-helical LK_{13} peptide disrupt the cell membrane (Figure 7b). The as-prepared assembly was tested on two Gram-negative bacteria (*P. aeruginosa*: ATCC 15442 and *E. coli*: ATCC 25922) and one Gram-positive bacterium (*S. aureus*: ATCC 6538). The MIC values follows the order: *P. aeruginosa* (8 μg peptide/mL) < *E. coli* (16 μg peptide/mL) < *S. aureus* (64 μg peptide/mL). The higher value for *S. aureus* is due to the absence of an outer membrane, and CS-PEG-LK_{13} continued to remain in the self-

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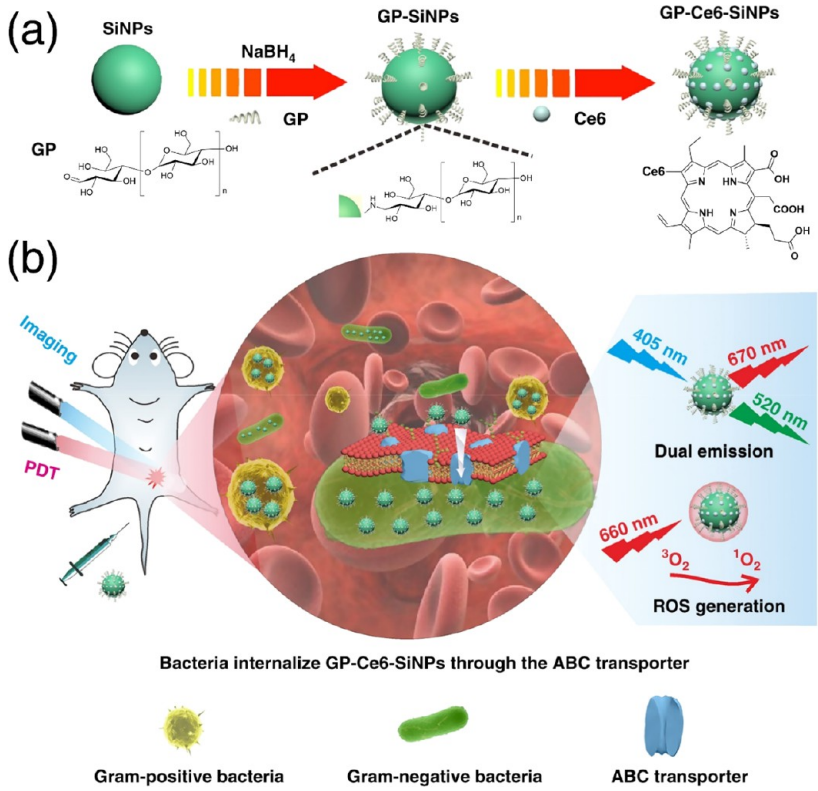

Figure 8. (a) GP-Ce6-SiNPs nanoagents synthesis. (b) Antimicrobial activity on Gram-negative and Gram-positive bacterial infections. Reproduced with permission from ref 249. Copyright 2019 Springer Nature.

assembled structure. Also, when the concentration was enhanced to 16 times the MIC, an antibacterial efficiency of 97.95% was achieved, while a control surface of LK_{13} peptide and the antibiotic tobramycin exhibited efficiencies of 41.58 and 45.50%, respectively.

Previous reports also suggest that cyclization positively impacts antimicrobial activity and selectivity. Mwangi et al. designed a cyclic peptide ZY4 (VCKRWKKWKRK-WKKWCV-NH_2) which forms a stable disulfide bridge and acts *in vitro* and *in vivo* against *P. aeruginosa* and *A. baumannii*, and the MIC values were in the ranges of 2.0−4.5 and 4.6−9.4 $\mu g\ mL^{-1}$, respectively.[248] The advantage of using ZY4 is that it comprised only 17 amino acids, and its smaller size also lead to a lower cost than that of large amino acids based peptides.

Tang et al. devoted their study to simultaneous imaging and treating the bacterial infections to carefully investigate the antimicrobial phenomenon.[249] The specially designed GP-Ce6-SiNPs nanoagents (where GP: glucose polymer, Ce6: chlorin e6, and SiNPs: silicon NPs) as shown in Figure 8. SiNPs and Ce6 provide fluorescence benefits, and GP works as the major microbial carbon source. Gram-positive bacteria such as *S. aureus* and *M. luteus* and Gram-negative bacteria such as *E. coli* and *P. aeruginosa* were tested. The antibacterial efficiencies were ∼98 and ∼96% against *S. aureus* and *P. aeruginosa*, respectively, and the improved results were due to the photodynamic effect of Ce6.

In an important study, Sun and co-workers developed robust daylight-driven rechargeable antibacterial (>99.9999%) and antiviral (>99.999%) nanofibrous membranes (RNMs).[250] The specifically designed membranes were able to produce and store biocidal reactive oxygen species (ROS) in daylight and release them in dim or dark conditions. The mechanism is illustrated in Figure 9a. The pathogens attack the surface of the membrane in the presence of light irradiation via various ROS such as hydroxyl radicals ($^{\bullet}OH$), superoxide ($^{\bullet}O^{2-}$), and hydrogen peroxide (H_2O_2). These subsequently rupture the DNA, RNA, and bacterial membrane parts leading to bacterial death and virus inactivation.

The results were also applied for bioprotective PPE application as shown in Figure 9b−g.[250] The BDCA-RNM (BD: 4-benzoyl benzoic acid, CA: chlorogenic acid, which both act as photobiocides) were fabricated on masks and protective suits followed by injection of 1×10^6 CFU of aerosols containing *E. coli* (diameter = 1−5 μm) which is also similar to that obtained from human sneezing or coughing. The results were compared at three locations, namely, a control area, a BDCA-RNM area, and a covered area. It can be observed from Figure 9d,g that the designed antimicrobial membranes provide robust protection against the pathogens. The control area suffered from bacterial growth and proliferation associated with the nonbiological function of traditional nonwoven materials.

Lázár et al. studied the effect of cross-resistance or collateral sensitivity monitored by decreased and increased sensitivity, respectively, on peptides due to the small-molecule antibiotics.[251] On the basis of the study of 60 *E. coli* strains toward 24 antimicrobial peptides, it has been concluded that cross-resistance is relatively rare, and a high frequency of collateral sensitivity is achieved.

Gao et al. prepared 3,6-*O*-sulfated chitosan (36S) to act against high-risk human papillomavirus (HPV) infection via Western blot assay.[252] These chitosan derivatives exhibit good selectivity and may directly or indirectly inhibit virus infection. In other words, it may directly bind to HPV or indirectly

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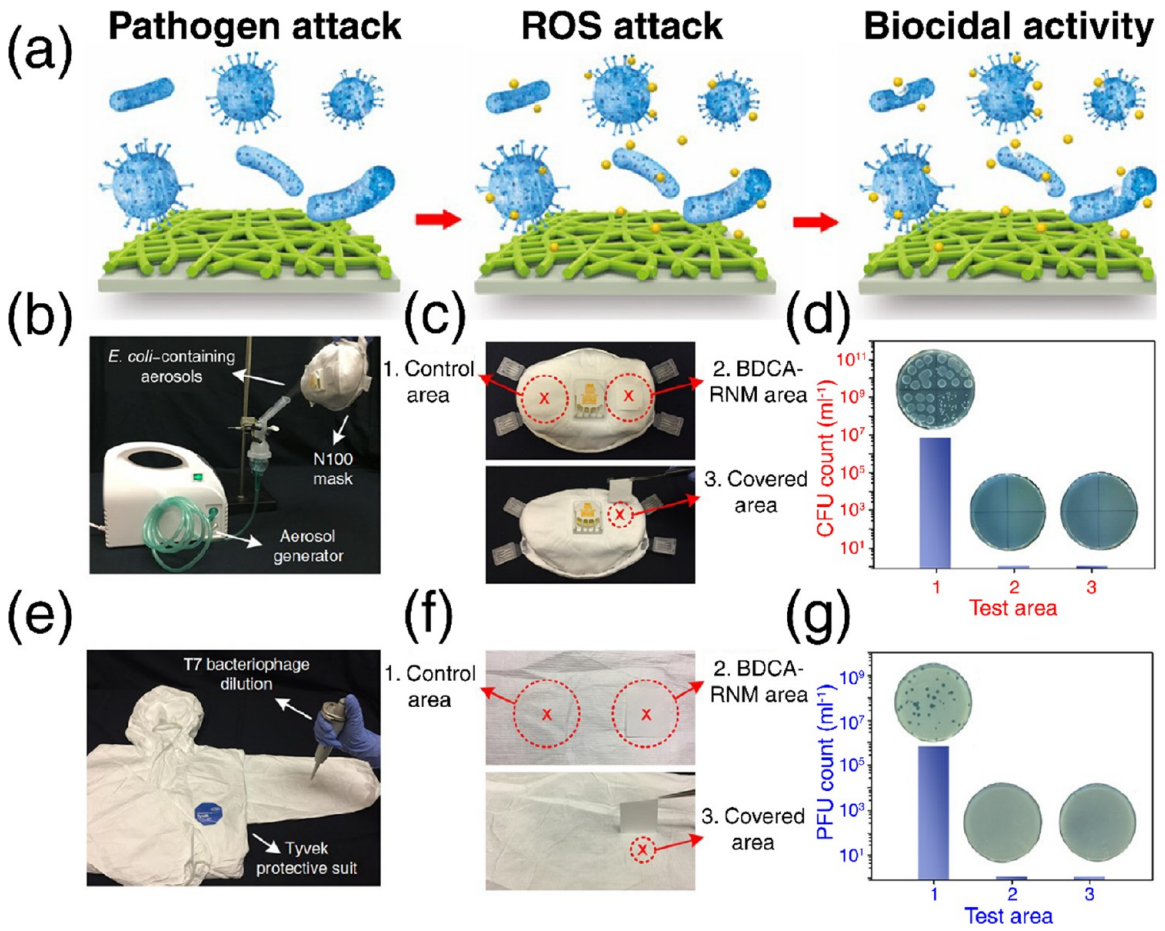

Figure 9. (a) Schematic demonstration of the biocidal functions of RNMs by releasing ROS. (b) Bacterial aerosol generation apparatus and the interception test by N100 mask. (c) Three selected test areas on the mask. (d) Relevant CFU count of E. *coli*. (e) Photograph showing the protective suit was loaded with T7 phage. (f) Three selected test areas on the protective suit. (g) Relevant PFU count of T7 phages. Reproduced with permission from ref 250. Copyright 2018 American Association for the Advancement of Science.

interfere with the host PI3K/Akt/mTOR pathway. In another study, Khalil et al. formulated γ-poly gamma-glutamic acid (PGA)−chitosan NPs to encapsulate adenovirus through ionic interaction.[253] The size and zeta potential of the NPs were 485.8 ± 2.3 nm and −23.7 ± 1.4 mV, respectively. The encapsulation efficiency was ∼92%. The cytotoxicity results showed a decrease to ∼75% at 5 mg mL^{-1}, while the lowest concentration of 0.156 mg mL^{-1} showed no cytotoxicity.

Yu et al. developed a guanidinothiosialoside-albumin conjugate mimicking mucin to act against influenza infection.[15] The improved virus capture and trapping was associated with the glycoconjugate bonds. More specifically, the neuraminidase present on the surface of influenza virus strongly bonded to the neomucin and was responsible for the antiviral activity. The virus cell viability was reduced to ∼50% at 10^5 nM conjugates, suggesting that mucin-based nanostructures have the potential to provide antiviral activity. Recently, Palmeira et al. identified GRP78 inhibitors to interfere with and inhibit SARS-CoV-2 infection.[254] The results indicated that the GRP78 gene expression was increased in SARS-CoV-2 (+) versus SARS-CoV-2 (−) samples. The associated mechanism is the reduced activity of ATPase on binding with the GRP78 nucleotide. Also, the epigallocatechin gallate (EGCG) present in green tea catechin showed antiviral activity for porcine circovirus type 2 (PCV2) as reported by Li et al.[14] The interaction between EGCG and PCV2 leads to the interference between the capsid-heparan sulfate. The EC_{50} (effective concentration at 50% of the maximal effect) was also calculated to be 37.79 ± 1.64 μM. The observed efficacy was no more potent than that of the conventional antivirals; however, the identification of the amino acid could lead to the further development of effective antivirus drugs. Kirsch et al. tried to understand the role of latency-associated nuclear antigen (LANA) against Kaposi's sarcoma herpes virus (KSHV).[255] The protein's ability to bind the viral genome and the host nucleosomes helped in its attachment. Thus, restricting the LANA−DNA interaction was responsible for the reduction of the host's viral DNA. The cytotoxicity study was also carried out on HEK293 and HepG2 cells and achieved maximum activities of 7 ± 6 and 20 ± 9%, respectively, at 100 μM. Apart from viruses, da Silva studied antifungal and antiprotozoal activity using rhamnolipids-based amino acids.[256] It was deduced that the cationic rhamnolipids showed activity against *Candida* species, while cationic as well as anionic rhamnolipids were potent against protozoal *Acanthamoeba castellanii* at a concentration of 4 mg L^{-1}. Long et al. explored the activity of a garlic oil nanoemulsion against *Penicillium italicum* for antifungal action.[257] They used an ultrasonication technique to synthesize the nanoemulsion with the size and concentration of 52.27 nm and 5.5%, respectively. This resulted in the destruction of the lipids, nucleic acids, and proteins of the microbe with an improved

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MIC of 0.01265% for the garlic oil nanoemulsion, compared to that of 3.7% for garlic oil alone.

ANTIBACTERIAL AND ANTIVIRAL PROPERTIES OF NANOMATERIALS

In the following sections, the role of emerging nanomaterials such as TiO_2, silver, and copper for the antibacterial and antiviral applications are discussed in detail.

TiO_2-Based Antimicrobial Materials. Development in the area of nanobiotechnology has resulted in a variety of materials that have potential applications as antibacterial materials.[38] TiO_2 is one of the most commonly used semiconductors for antimicrobial applications in contemporary literature.[258−260] The unique property of TiO_2 is useful for disinfection microorganisms including bacteria, fungi, and virus.[261−263] Biosynthesized TiO_2 NPs were found to be most effective compared to a chemical process for antimicrobial applications due to low cost, nontoxicity, and high stability.[264] Recently, coatings of semiconductor-based photocatalysts like TiO_2 over surfaces were studied as antibacterial surfaces and evaluated for the decomposition of various microorganism like bacteria, fungi, and virus.[265,266] The decomposition microorganisms principally is due to the light-harvesting ability of TiO_2.[261] Efficacy of TiO_2 as an antimicrobial agent depends on several parameters: (i) the size and shape of the TiO_2 nanocrystal, (ii) the stability of the TiO_2 nanocrystals (iii) the extent of electron−hole separation, (iv) reduced charge carrier recombination, and (v) the extended absorption in the visible region. Crystallite phase-dependent TiO_2 film was investigated for deactivation of microorganisms (*Streptococcus sanguinis*, *Actinomyces naeslundii*, and *Fusobacterium nucleatum*) by Pantaroto et al. under UV light exposure.[267] Anatase, rutile, and a mixture of anatase and rutile films were obtained using a radio frequency magnetron-sputtering technique. Antibacterial activity was investigated for a period of 16.5 h with a period of 1 h of UV-A light irradiation on the TiO_2 surface. The greatest antibacterial activity was obtained with the mixture film (anatase and rutile), followed by anatase and rutile films, respectively.

The excellent photocatalytic activity of the mixture is probably due to the Type II band gap alignment which significantly reduces electron and hole pair separation. As a result, excess production of ROS on the TiO_2 surface inactivates the microorganism. Enhancement of the antimicrobial activity against *E. coli* and *S. aureus* was reported by Al-Jawad et al. upon Fe doping within TiO_2 films under UV light exposure.[268] Deposition of TiO_2 film over glass slide was carried out via a spin coating method using titanium tetra isopropoxide as the titanium precursor. The crystallite size of TiO_2 film was found to be 19−26 nm; 3, 4, 5, and 6 vol % Fe doping was achieved within the film using ferric nitrate as the Fe precursor. The presence of Fe within the TiO_2 lattice improved absorption of radiant energy, which significantly enhances ROS at the film surface leads to the decomposition of bacterial protein and DNA under UV illumination. The optimum activity was observed for 6% Fe-TiO_2 films against *S. aureus* (97%) and *E. coli* (100%) using 1 h of UV light exposure. Au-capped anatase TiO_2 (average size 12−18 nm) was found to be good antimicrobial coating material in comparison to its counterpart under UV LED irradiation.[269] Here, both TiO_2 and Au/TiO_2 sprayed on a glass slide and improvement in antibacterial activity (as tested against *Bacillus megaterium* and *E. coli*) was observed. Au-coated TiO_2 was found to be an efficient antimicrobial agent for the sterilization of *E. coli*. Here, the presence of Au over a TiO_2 surface facilitates charge carrier separation and ROS production, which is responsible for pronounced antimicrobial activity. Wunderlich et al. reported TiO_2-coated surfaces for antimicrobial application under UV-A light exposure.[270] They deposited a titanium dioxide layer over a glass slide using 8 vol % tetraisopropylorthotitanat (TPOT, $C_{12}H_{28}O_4Ti$) as the Ti precursor via a sol−gel method. Different strains (*Aspergillus niger*, *Bacillus atrophaeus*, *Kocuria rhizophila*) were identified to monitor antimicrobial activity on the TiO_2-coated surface. An inactivation of about 3.4 $\log_{10}$ was reported using titanium dioxide after 4 h of UV-A illumination for *K. rhizophila*. Several parameters (relative humidity, inoculation density, and radiation intensity) were investigated on the antimicrobial efficiency. The highest inactivation (5.2 $\log_{10}$) observed (85% relative humidity) confirms the role of relative humidity directly upon the antimicrobial activity of titanium dioxide. Improvement in photocatalytic is observed at higher inoculation density (10^5 CFU), while increased in radiation intensity increases antimicrobial activity.

Bulk polymer template was also used by Wintermantel et al. for thin-film TiO_2 coating to ensure its surface for antimicrobial application.[266] Different titania content over polymer matrices was studied for antimicrobial activity and found the order 15 wt % > 10 wt % > 2 wt % > 0 wt %. Medical polypropylene coated with nano TiO_2 (21 nm) nanocomposite were prepared via melt compounding in a corotating twin-screw extruder (Berstorff ZE25Ax45D-UTX, Krauss Maffei Berstorff) with an optimized screw configuration. It was reported that the polymer-embedded TiO_2 particle is very much efficient for *E. coli* bacteria inactivation under UV irradiation. Similar antimicrobial activity was reported by Xing et al. using TiO_2 incorporated polyethylene (PE)-based film. Here, anatase TiO_2 (10−20 nm) incorporation over polyethylene (PE)-based film was performed using a twin-screw extruder, with the average thickness (40 ± 3) mm. UV mediated significant reduction of *E. coli* (89.3%) and *S. aureus* (95.2%) was observed within 60 min.[265] Water-processable PVA was used as a support for the decoration of Cu_2O-TiO_2/rGO nanocomposite using solution casting technique.[271] Uniform spherical size (17 nm) of TiO_2 and Cu_2O NPs were distributed over reduced GO surface (as evident from TEM study). Polymer nanocomposite (Cu_2O-TiO_2/rGO) films (60 ± 6) μm exhibits antimicrobial activity against different pathogens (*S. aureus*, *Streptococcus oralis*, *E. coli*, and *P. aeruginosa*) under a fluorescent bulb (36 W) with an incubation period of 24 h, and it was found to be most effective against *S. aureus* one under optimized conditions (Figure 10). Here, doping with copper improved visible light absorption ability of TiO_2, and the support of reduced graphene oxide improved the charge carrier (generated from Cu_2O/TiO_2) separation to accelerate photocatalytic degradation of microorganisms. Yang et al. reported TiO_2 thin film decorated with plasmonic silver on a silicon wafer (decorated via spin-coating technique) was successful against Gram-negative bacteria (*Escherichia coli* ATCC 29425) under UV illumination (8 W).[272] The different molar composition of Ti^{4+} to Ag^+ of 50:1 (SG1), 20:1(SG2), 10:1(SG3) and 5:1(SG4) were used for antimicrobial activity and effective results were obtained SG4, where 100% bacterial killing was observed under 1 h UV exposure. Improved antimicrobial activity in the presence of Ag was ascribed photoactive property of Ag ions and photo-

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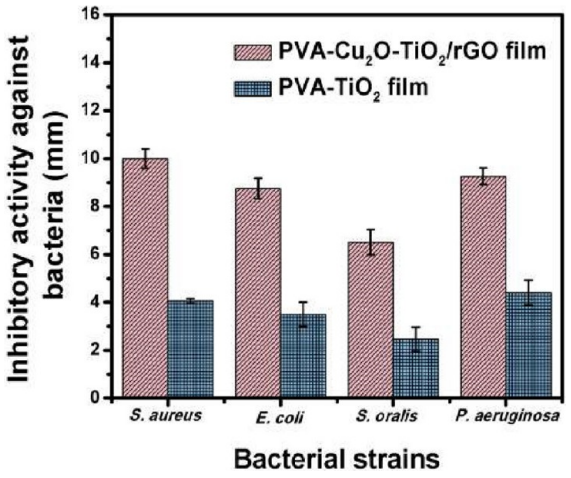

Figure 10. Inhibitory activity of PVA-TiO_2 and PVA-Cu_2O-TiO_2/rGO nanocomposite films against *S. aureus*, *E. coli*, *S. oralis*, and *P. aeruginosa*. Reproduced with permission from ref 271. Copyright 2018 Elsevier.

chemical reaction that enzymatic function leading to inactivation of bacteria. Incorporation of anatase TiO_2 NP (80 nm) into an isotactic polypropylene matrix was excellent microorganism activity against Gram-negative (*P. aeruginosa*) and positive (*E. faecalis*) bacteria upon light irradiation.[273] The excellent activity of nanocomposite in comparison to oxide one is due to favorable contact that changes the nature of the TiO_2 for better proximity with the pathogen. Wong et al. reported antibacterial activity (*Bacillus pumilus*) upon dip-coating TiO_2 films on stainless steel.[274] Incorporation of TiO_2 on a plastic film found to have antifungal activity against Penicillium expansum as the test organism.[275] Bulut et al. coated anatase TiO_2 film over ceramic brackets via a sol–gel method.[276] Reduction efficiencies 98% (*S. mutans*) and 93% (*C. albicans*) were observed under UV-A illumination. Pirvu et al. synthesized TiO_2 nanotube over Ti foil and further modified with torularhodin using a bioadhesive polydopamine.[277] The modified TiO_2/Ti surface was tested excellent antibacterial activity against different human pathogens like *E. coli*, *S. aureus*, *E. faecalis*, *P. aeruginosa*, and *B. subtilis* (Figure 11).

The mechanism associated with the effective antimicrobial property of TiO_2 is reported in several pieces of literature.[278] Wide band gap TiO_2 (3.2 eV) generates electron and hole pairs under suitable irradiation. Photogenerated electron and hole pairs come to the surface and react with adsorbed species to generates different ROS. Now, photogenerated ROS reacts with microorganism (bacteria/fungi/virus) in a different mechanism (Figure 12).[279,280] In one pathway, it may react with the cell wall and disrupt it, while in another pathway it can damage the cell membrane. Some works also reported inactivation of the respiratory chain system and signaling network. Therefore, the size of TiO_2 as well as the nature of the interaction with the TiO_2 surface with bacteria/virus surface very important for the use of TiO_2 as a microrepellent surface due to its nanoscopic features.[264,281] The nanoscale behavior of TiO_2 NP modulates the surface to volume ratio, which helps in maximizing interaction to produce ROS, while the minimal size of NP helps cell wall and cell membrane disruption via intracellular oxidative damage.

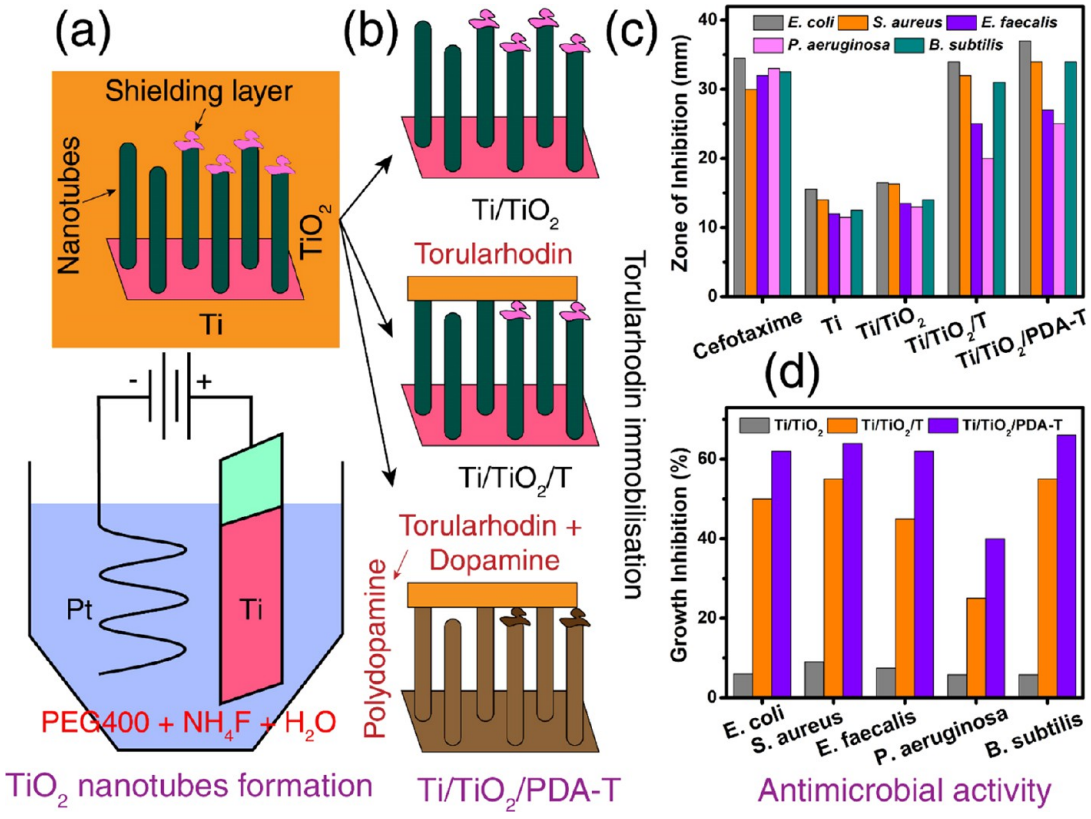

Figure 11. (a, b) Scheme for the synthesis of TiO_2/Ti by torularhodin bioinspired surface modification. (c, d) Antimicrobial activity. (Here, the approximate values are shown for comparison.) Reproduced with permission from ref 277. Copyright 2016 Elsevier.

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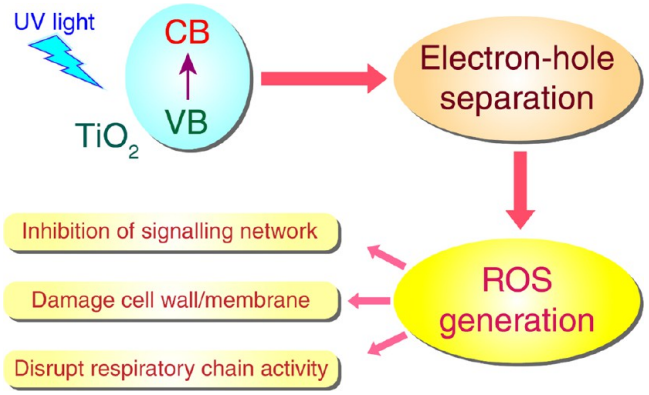

Figure 12. Proposed different pathways of TiO_2 based antimicrobial activity.

Antimicrobial activity of TiO_2 was reported for *Pseudomonas aeruginosa* PAO1 cells under UV light illumination. Here, antimicrobial activity is observed because of the inhibition of metabolic function and regulatory pathways by TiO_2.[282] Chitosan decorated TiO_2 NPs film was reported an effective antimicrobial agent for a variety of strains (*E. coli*, *S. aureus*, *C. albicans*, and *A. niger*) within 12 h under visible light illumination.[283] Such a nanobio film has an impact on food-packing applications. Antiviral activity of TiO_2 was reported by Nakao et al. under UV light illumination.[284] Inactivation of influenza virus (reduction of approximately 4 $\log_{10}$) was observed within 8 h at very low intensity (0.01 mW cm^{-2}). A probable mechanism for influenza virus inactivation was due to the generation of different oxidative species ($^{\bullet}OH$ and O_2^-), which subsequently target DNA and RNA, results in the damage of viral protein. Modification of TiO_2 with Cu(II) was reported as an excellent means of directing visible light toward deactivation of Bacteriophage $Q\beta$ used as a model virus.[285] Deactivation of 99% of the virus was observed within 1 h under a fluorescent lamp. Here, the presence of Cu(II) over TiO_2 facilitates charge carrier separation via IFCT to form Cu(I), which regenerates via multielectron reduction processes. Therefore, a hole of TiO_2 and Cu(I) simultaneously attack membrane, protein, DNA and RNA and leads to their death. Dual antibacterial (*E. coli*) and antiviral (virus HSV-1) activity were reported by Hajkova et al. using chemical vapor deposition TiO_2 film on glass substrates.[286] Deposition of TiO_2 film was carried out in a radio frequency capacitive coupled homemade planar PECVD reactor. Antibacterial and antiviral activities of 100% were observed by TiO_2 film under 6 h UV illumination.

Antimicrobial Aspects of Photocatalyst. For the photocatalytic disinfection of water from microorganisms, it is essential to develop efficient photocatalysts that exhibit high antimicrobial activity under solar irradiation. Different types of photocatalysts, e.g., ZnO, CuO, TiO_2, Fe_3O_4, and carbon-based materials in pure as well as composite form, have been developed for environmental and photocatalytic water disinfection applications.[146,278,287−301] Plasmonic Ag NPs decorated with ZnO were used by Yudha et al. for inactivation of *E. coli* and degradation of rhodamine B in water.[302] Here, the presence of Ag improved the inactivation of *E. coli* and degradation of rhodamine B in comparison to pristine ZnO under UV illumination. Polydopamine decorated with ZnO nanorods has been reported to have an excellent antimicrobial property as well as to decontaminate organic pollutants (methylene blue) under UV LED illumination.[303] Photocatalytic performances of TiO_2 and Au/TiO_2 were studied by Armelao et al. toward decomposition of azo-dye Plasmocorinth B and elimination of *B. subtilis*.[263] The magnetically separable heterostructure of $Ag_3PO_4/TiO_2/Fe_3O_4$ was efficient for dual applications of photodegradation of acid orange 7 (AO7) and decontamination of *E. coli* cells under visible-light irradiation.[304] Efficient charge carrier separation at the interface facilitates electron and hole separation, which is the main driving force toward the degradation of pollutants and decontamination of microorganism in water. In another work, Cho et al. developed Ag@CeO_2 nanocomposites and assessed their antimicrobial activity under visible-light irradiation.[305] Excellent antimicrobial activity toward *E. coli* O157:H7 and *P. aeruginosa* and photocatalytic degradation of organic dyes under visible light were observed due to efficient electron and hole separation. Recently, Siddiqui et al. synthesized copper oxide nanoflowers (CuO-NFs) and reported excellent performance for the degradation of methylene blue as well as inactivation of microorganisms (*E. coli*).[306]

Silver-Based Antimicrobial Materials. Among the studied metals, Ag and Ag-containing materials, owing to their unique properties, have gained wide attention for potential medicinal applications as antibacterial, antifungal, and antiviral materials.[41−43] Silver is a soft, white, shiny metal exhibiting high electrical and thermal conductivity. Apart from therapeutic purposes, silver-based materials have been employed for different applications including as constituents of water purification and dental hygiene products. It is worth mentioning that Ag nanostructures provide comparable antimicrobial activities to those provided by Ag ions.[44−46] Furthermore, Ag and its oxide (Ag_2O) NPs have crucial antibacterial and antimicrobial applications in tissue engineering, wound healing materials, dentistry, textile manufacturing, water disinfection, and food packaging. Their antimicrobial mechanisms have been investigated in different studies, according to which during physical interaction between Ag NPs and microorganisms the Ag ions interact with the peptidoglycan cell wall of bacteria, which leads to structural variation, as a result of which membrane permeability increases leading to cell death.[307−310] Ag nanomaterials also help in preventing DNA replication by interacting with bacterial proteins through exposed sulfhydryl groups. Interactions between bacterial DNA and Ag_2O results in a loss of replication ability of DNA.[310−315] The antiviral response of Ag NPs (98%) against HIV-1 is documented as being significantly better than that of Au NPs (6−20%). Hence, we see that Ag is an important and promising solution for a range of microbes and the mechanism of antimicrobial activity differs for various Ag-based materials.

Several simple and effective techniques have been adopted toward achieving different Ag nanostructures with controlled physicochemical properties. Usually, the higher surface-to-atom ratio of smaller Ag NPs favors their bacterial membrane interaction, and these small NPs release greater amount of Ag^+ with accelerated kinetics, which enhances their interaction efficiency with the bacteria's subcellular organelles and also generates more ROS in the process.[316,317] Furthermore, the antimicrobial ability is also significantly affected by other physio-chemical features of NPs such as morphology, oxidation states, and the aggregation/dissolution state.[222,318,319] Hence, Ag NPs of different shapes such as beads, mats, rods,

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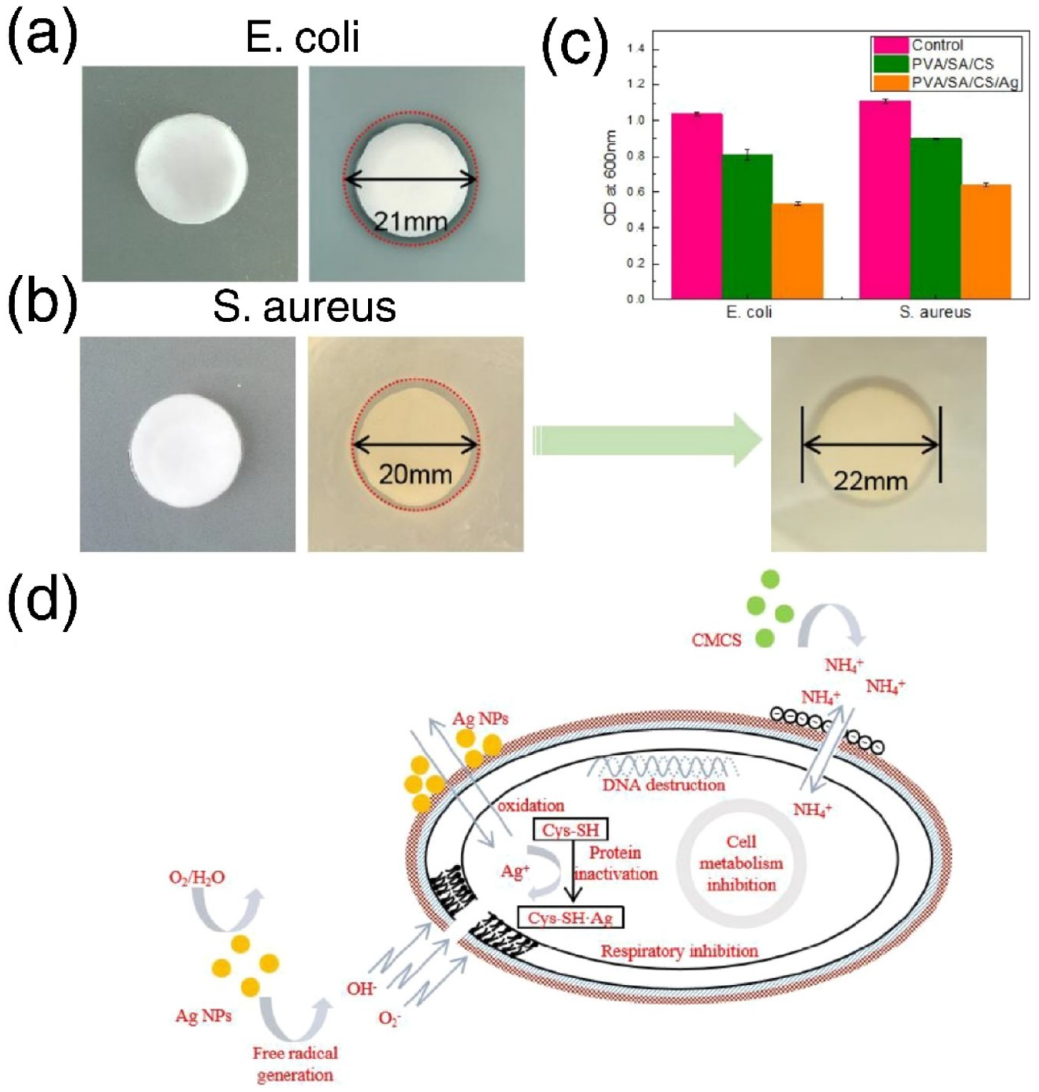

Figure 13. Antibacterial activity of different hydrogels using (a) *E. coli* and (b) *S. aureus*. (c) Optical density at 600 nm measured 24 h after incubating with different hydrogels. (d) Antibacterial mechanism of AgNPs. Reproduced with permission from 312. Copyright 2020 Elsevier.

nanoprisms, and sheets are being reported for their specific antibacterial effects. Ag NPs based antimicrobial wound therapy has proven to be an effective tool to cure wounds and is now widely used in wound healing products. Recently, smaller NPs have been observed to cause a higher level of toxicity; therefore, there are open research gaps which must be filled for reliability and widespread utility.[320−322] Plenty of researchers are working toward developing biomaterials and scaffolds with embedded metallic NPs.[230] Herein, we will discuss some of the promising Ag-based systems developed for their antimicrobial properties.

Jo et al. proposed a new antibacterial coating technique which is surface-independent and involves the fusion of mussel adhesive proteins (MAP) to Ag-binding peptides and is capable of synthesizing Ag NPs with wide antibacterial response.[42] The synthesis can be achieved under mild conditions in which a good adhesive coating on a substrate takes place with the help of a sticky recombinant fusion protein, followed by the production of Ag NPs on the coated surface. Thus, synthesized Ag NPs showed good cytocompatibility with mammalian cells and noticeable antibacterial performance against both Gram-positive and Gram-negative bacteria. In this process, MAP-Ag fusion proteins supply the hybrid environment for Ag NPs and mediate their interactions with the surrounding environment. Hence, this simple-yet-effective coating technique has a potential as a versatile technique in the treatment of bacterial infection and can be extended to a variety of substrates owing to its surface-independent property.

In another report, Chen et al. developed an antibacterial wound dressing based on Ag-loaded PVA/SA/CMCS hydrogel.[312] Herein, AgNPs were produced by a greener and safer method, i.e., *in situ* reduction with sodium alginate (SA). Furthermore, the particle size was small and homogeneous throughout the mass, which is suitable for good antibacterial activity and stable performance. The Ag-loaded hydrogel, owing to its uniform pores, shows excellent water absorption and/or retention, which can absorb most of the wound exudate and also help maintain a moist environment around the wound. Overall, Ag-loaded hydrogel is an ideal wound dressing material (Figure 13), with good antibacterial activity and biocompatibility; it is also better than the Ag-free hydrogel. Interestingly, the antibacterial performance of the Ag-loaded

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hydrogel is sustainable and significantly better, which helps avoid bacterial infection and keeps the wound sterile.

D'Lima et al. reported Ag/Ag_2O NPs by employing a biosynthesis approach using a novel strain of *Kitasatospora albolonga*.[316] The microscopic and structural analysis of obtained material reveals a spherical shaped $Ag–Ag_2O$ hybrid core–shell (Ag_2O@Ag) structured NPs (Figure 14a). Though

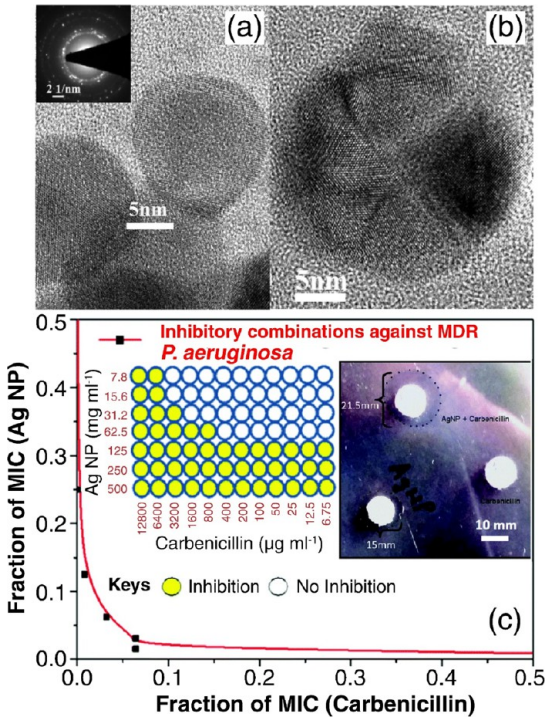

Figure 14. (a) HRTEM micrograph of the two identified features in the biosynthesized hybrid AgNPs showing a phase-separated core–shell structure with a crystalline shell (Inset). (b) Selected area electron diffraction (SAED) pattern of the sample AgNPs with faceted polycrystalline secondary growth. (c) Fractional inhibition concentration (FIC) distribution depicting synergy between AgNPs and carbenicillin against MDR *P. aeruginosa*. The FIC value varies from 0.080 to 0.095, 0.095, 0.13, and 0.25 for points from left to right showing a transition from a synergistic nature at lower concentrations of AgNPs to an additive nature at higher concentrations. Inset: Zone of inhibition. Reproduced with permission from ref 316. Copyright 2020 The Royal Society of Chemistry.

these hybrid NPs had shown antimicrobial activity independently, however, when combined with carbenicillin, it showed an improved toxic synergetic effect on multi-drug-resistant *P. aeruginosa* (MDRP) at low concentrations (Figure 14b). The fractional inhibition concentration is presented in Figure 14c. Furthermore, minute additions of Ag NPs lead to a significantly enhanced potency of the antimicrobial species. This research could lead to an effective choice against multi-drug-resistant bacteria and pave the pathway toward simple and effective solutions to critical medical issues.

According to Tao et al., bimetallic silver–iron NPs (Ag–Fe NPs) can lead to attractive antimicrobial materials because of their multifunctional properties. The antimicrobial performance of Ag–Fe NPs is affected significantly by alloying structure, particle size, and composition, but their preparation is a challenge due to the large difference in lattice constants of the two elements. An ultrasonic-assisted *in situ* reduction method was used to prepare Ag–Fe/graphene-based cellular monolith (Ag–Fe/GCM) materials with a well-defined alloy structure, ultrafine size, and abundant hierarchical structure. They found that the antimicrobial activity of such materials decreased, but the stability of Ag improved with the increase of Fe content within a certain range. The more active Fe in alloys can protect the Ag from oxidation, which reduces the release of Ag^+ (Figure 15a). However, the release of Fe ions led to more generation of ROS compared with Ag/GCM, which maintained a high antibacterial activity. By adjusting the Fe content, an Ag–Fe/GCM material with optimal performance was achieved. The Ag–Fe/GCM products with different Ag/Fe ratios of 3:1, 1:1, and 1:3 were obtained (Figure 15b). This work not only provides a method for preparing Ag–Fe alloys but also is useful for understanding its antimicrobial mechanism. Moreover, the Ag–Fe/GCM material also performs well in the filtering of bacterial pathogens and is a highly promising material for advanced antimicrobial and water-treatment applications.[44]

In another pioneering work by Kruk et al., antimicrobial coatings was designed using ultrathin polyelectrolyte films containing Ag Nps. In this process, polyethylenimine (PEI) and poly(sodium 4-styrenesulfonate) (PSS) were used as polycation and polyanions, respectively, and in combination with negatively charged AgNPs, resulted in polyelectrolyte-Ag nanocomposite coatings. The properties of formed film such as thickness, mass, structure and morphology were measured by various techniques. The successful fabrication of alternative and consecutive layers was confirmed through a systematic increase in UV–Vis absorption and the adhesion of bacteria cell on the film surface was checked by luminometry measurement. In these tests, three different Gram-negative bacterial strains were used: *E. coli*, *Aeromonas hydrophila*, and *Asaia lannenesis*, which usually display good adhesive nature. The results conclude notable antimicrobial activity of nanocomposite films, which makes them suitable to combat medical challenges including antimicrobial coatings.[319]

Kumar et al. described a green as well as an ecofriendly chemical approach to synthesize paint embedded with Ag NPs from easily available household paint through a one-pot synthesis method.[320] They employed a naturally arising oxidative drying procedure in oils, which involves free-radical exchange as the elementary mechanism for reduction of metal salts and dispersion of metal NPs in the oil media, in absence of any external reducing or stabilizing species. Such well-dispersed metal-NPs-in-oil dispersions can be used directly on various kind of surfaces as glass, steel, wood, and polymers. The Ag-NP-paint-loaded surface showed remarkable antimicrobial properties by killing both Gram-positive human pathogens (*S. aureus*) and Gram-negative bacteria (*E. coli*). This process is facile and versatile, which can be extended to a variety of microbes.

Other than these examples, various Ag-based composites and alloys have been used in antimicrobial applications. Wang et al. described the antimicrobial properties of PVA-modified packaged films of bacterial nanocellulose incorporating with Ag Nps.[310] Ali and co-workers used fractionated phytochemicals to produce Ag NPs for antimicrobial activity against *S. aureus* and *E. coli* bacteria.[46] Mokabber et al. developed a Ag-containing calcium phosphate (Ag/Ca–P) coating by electrochemical deposition technique over Ti substrates and did a thorough study on their biocompatibility and antimicrobial activity.[309] Cobos et al. synthesized a graphene oxide–Ag NPs hybrid and studied their antimicrobial properties for different

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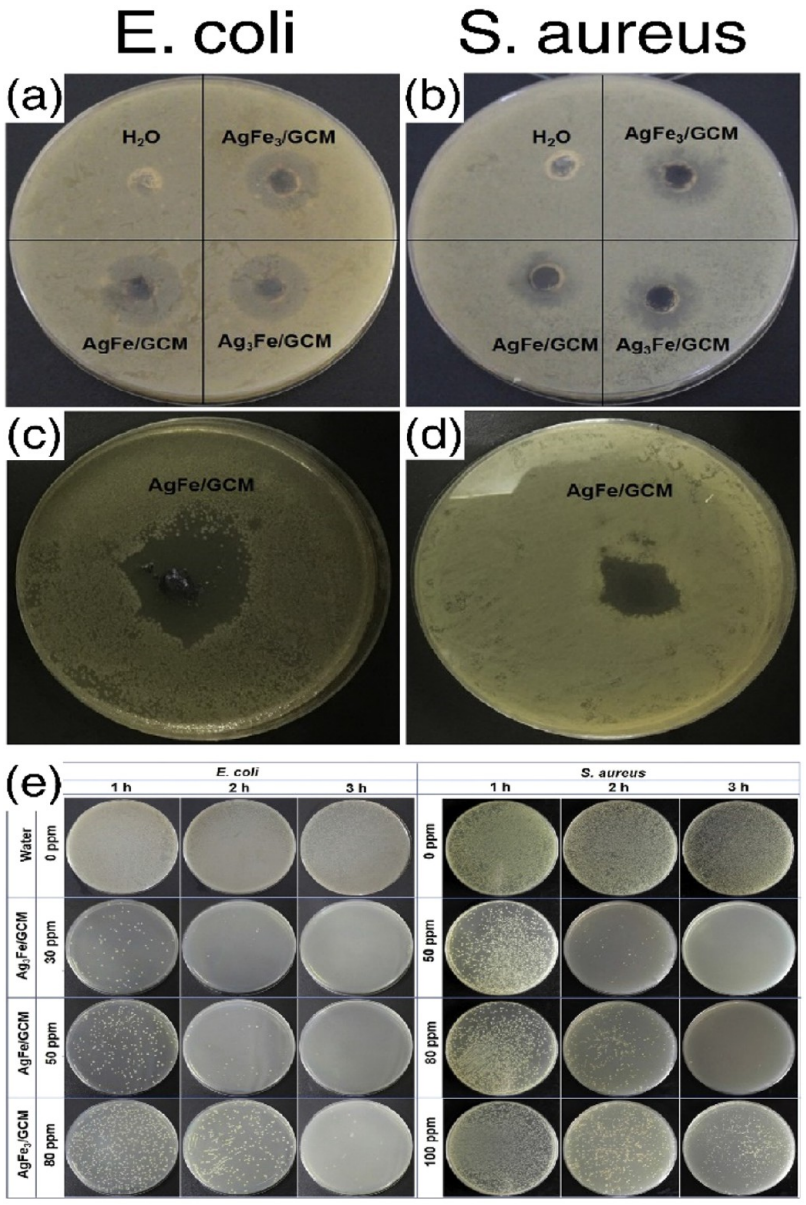

Figure 15. Photographs of (a) *E. coli* and (b) *S. aureus* grown around 50 ppm of AgFe/GCM products on the plates, (c) *E. coli* and (d) *S. aureus* grown around 0.3 mg AgFe/GCM powder. (e) Inhibition of colonies of *E. coli* (left column) and *S. aureus* (right column) treated with AgeFe/GCM for 1−3 h. Reproduced with permission from ref 44. Copyright 2020 Elsevier.

microbial species.[311] Qi and co-workers developed a novel metal NPs@MOFs system (metal: Ag or Cu; Zn-BIF: MOF framework of zinc-based boron imidazolate) to study its catalytic synergistic antimicrobial activity.[314] Similarly, various other systems based on Ag ion/metal have been proposed to combat microbial challenges. From the above examples, it can be surmised that Ag is widely utilized against a broad spectrum of species of bacteria (>650 pathogens) owing to its relatively low toxicity toward mammalian cells. Ag-based NPs and composites are also increasingly used for infection treatment due to their notable antimicrobial properties. However, even after the significant progress, the antimicrobial mechanism of Ag-based materials is not yet fully understood. So far, two different mechanisms, i.e., contact and leaching killing, have been proposed by researchers. In the first process, bacteria are being killed by direct contact of metallic AgNPs by attaching to its cell wall, forming pits in the cell membrane, followed by cytoplasm penetration, which ultimately causes cell death.[321,322] The other process involves the gradual release of Ag^+ ions followed by their interaction with proteins' thiol groups, inhibiting cell respiration and DNA replication.[309] Recent progress in Ag or Ag oxide NPs based wound dressings shows a remarkable improvement over traditional dressings, which are used to heal wounds. Moreover, recently some Ag-based dressings have been accepted as an alternate to antibiotics in curing wound infection. Hence, Ag or Ag-based nanomaterials can be effective choices for a range of antimicrobial coatings and related applications.

Though the literature of Ag NPs is primarily focused on antimicrobial activity against bacteria, Ag has also been demonstrated as an effective agent against different families of viruses including HIV, herpes simplex virus, respiratory syncytial virus, hepatitis, and monkeypox.[323−327] It has been shown that metal NPs offer numerous possibilities in

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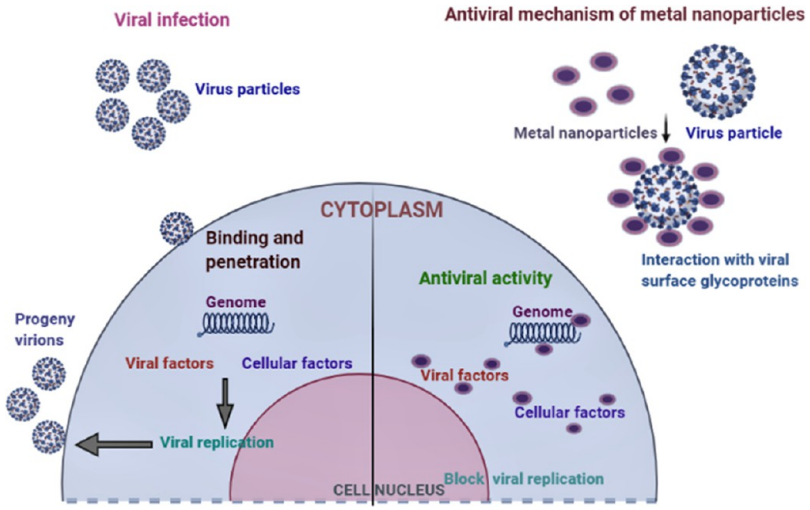

Figure 16. Schematic model of a virus infecting a eukaryotic cell and antiviral mechanism of metal NPs. Reproduced with permission from ref 332. Copyright 2011 MDPI, Basel, Switzerland. Recreated with BioRender.com.

developing novel antiviral therapies owing to their ability to attack a broader range of targets in the virus with the minimum possibility to develop resistance compared to conventional antiviral species. In particular, Ag NPs have shown great potential as antiviral agents against viruses. According to a recent article by Sarkar, the possible antiviral mechanism of Ag NPs involves their binding to surface glycoproteins of RNA viruses which prevent the fusion of the virus to host cell.[328] They also proposed a novel antiviral therapy which can be effective in killing COVID-19 virus with minimal side effects. In another report by Dung et al., Ag NPs were found to be effective against African swine fever virus (ASFV). Their study demonstrates a significant drop in viral contamination after spraying of Ag NPs.[329] Sharma et al. produced Ag NPs from medicinal plants (*Andrographis paniculata*, *Phyllanthus niruri*, and *Tinospora cordifolia*) via a green method and evaluated their antiviral properties against chikungunya virus.[289] The 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide (MTT) essay results reveal that Ag NPs synthesized from *A. paniculata* showed the maximum inhibition of virus activity. Orlowski et al. prepared tannic acid modified Ag NPs which showed antiviral activities against herpes simplex virus type 2 (HSV-2) infection.[330] They prepared different sized Ag NPs of 13, 33, and 46 nm which can significantly reduce HSV-2 infectivity both *in vitro* and *in vivo*. In their study, smaller Ag NPs led to the generation of cytokines and chemokines, which are important for antiviral response, and they concluded that tannic acid modified Ag NPs have great potential for microbicides used in curing of herpesvirus infections. Mori et al. produced a Ag NPs/chitosan (NPs/CS) composite with antiviral activity against H1N1 influenza A virus.[331] In their study, they compared the TCID50 ratio of viral samples treated with the composites to untreated suspensions, and in this way, they evaluated the antiviral response of Ag NPs/CS composites. Similarly, some other reports also suggest that Ag NPs can be effective against different families of viruses and by controlling their size, shape, and morphologies, they can be combined with many other materials to produce fascinating composites with improved antiviral properties. The research paves the path for next-generation antiviral agents including COVID-19.

A general graphical schematic demonstrating virus infection of a eukaryotic cell and its antiviral mechanism has been shown in Figure 16.[332]

Copper-Based Coating as an Antimicrobial Disinfectant. As far as availability of copper is concerned, it is the oldest and 26th most abundant element found in the earth's crust whose usage dates back to 9000 BC.[333] The antiseptic properties of copper and its beneficial effect on health already finds its mention in the ancient textbooks of Ayurveda and Hippocrates.[333] Although the emergence of antibiotics in the 1930s slowed down the research in the field of copper-derived antimicrobial agents the emergence of multi-drug-resistant bacteria, the period of 1980−1990s further bolstered research in developing antimicrobial agents using copper and its alloys. Antibiotics function by typically targeting a particular biochemical process, but in the due course, bacteria resists by deactivating the antibiotic or altering the targeted site (adaptive modifications).[334] In contrast, Cu targets multiple cellular processes occurring in bacteria, displaying an effect commonly known as a pleiotropic effect which abates resistance evolution. Copper gained massive attention in the medical community when copper and its alloys were recognized as the first effective metallic antimicrobial agent by US Environmental Protection Agency (EPA) officially in 2008, because of its excellent ability to kill 99.9% of the pathogenic bacteria just within 2 h, via "contact killing".[335] This encouraged the EPA to register nearly 300 copper surfaces as antimicrobial products for cleaning and disinfection applications.[334−336] There has been a surge in patents granted on antimicrobial coatings of copper and research activities in the past 20 years. On further investigation, it has been found that copper has an excellent efficacy against a range of pathogenic microorganisms such as Gram-positive bacteria such as *S. aureus*,[337−340] *Clostridium difficile*,[338,341,342] and *B. subtili*,[340] Gram-negative bacteria such as *E. coli*,[339,340,343,344] *P. aeruginosa*,[345] and *Legionella pneumophila*[346], and viruses. Motivated by the superior antimicrobial properties of copper, it finds applications in numerous ways in our life right from the construction sector to the healthcare sector for preventing infections in hospitals. Where the application of copper is concerned in day to day life, as disinfectant surface copper finds usage in air-conditioning systems, antifouling water

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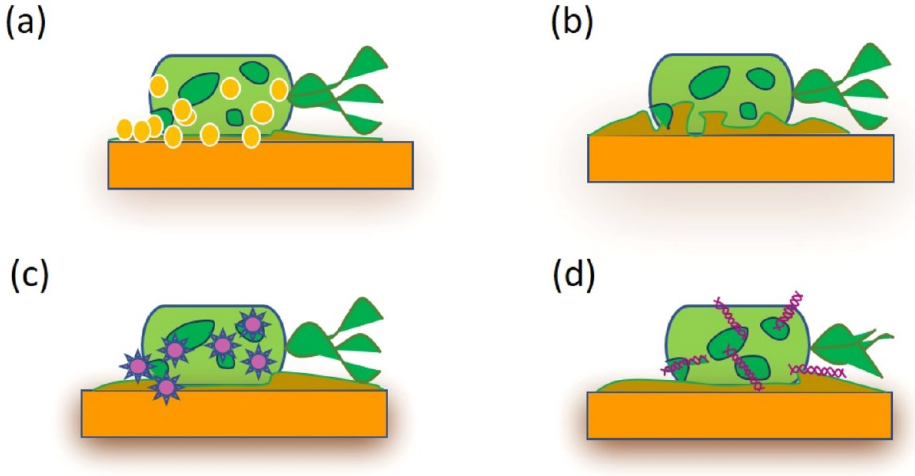

Figure 17. Schematic illustrations for contact killing: (a) Cell damage caused due to copper dissolved from the copper surface. (b) Loss of membrane potential and cytoplasmic content due to cell membrane rupture by copper and other stress phenomena. (c) Reactive oxygen species generation and subsequent cell damage by copper ions. (d) Degradation of genomic and plasmid DNA.[336]

treatment membranes, heating ventilation, and antibacterial textiles, so it becomes necessary to gain an insight into the mechanism of antimicrobial activity of Cu to improve its efficacy as a microbial agent for varying applications. Although its exact mechanism has not been elucidated, based on past several studies available in the literature, the antimicrobial effect of Cu is mediated by various factors such as physical properties (NPs or ion), chemical properties (the oxidation state of Cu), Cu concentration, accessibility of microbes to copper surfaces, nature of the application (dry or wet), operating temperature, and contaminants or buffers present in the chemical environment.[347] Primarily, there are two mechanisms that have been proposed to explain how copper surfaces interact with the microbes: (a) membrane depolarization and (b) ROS generation. Membrane depolarization is the widely proposed mechanism responsible for killing of bacteria by Cu ions.[348,349] Active bacteria has of a membrane induced potential difference of nearly 100−200 mV between the inside and outside the cell, whereas the interior of the cell is at a less negative potential. These Cu ions reduce the potential difference by binding with bacterial cells' negatively charged domains on both the inside and outside of the cell which promotes membrane depolarization, thus making the membranes leaky or ruptured too if the potential difference becomes zero. This type of mechanism has been reported in the Gram-positive and Gram-negative bacteria where Cu ions bind to the peptidoglycans, lipopolysaccharides, or carboxylic groups.[350,351] ROS generation is the hallmark of Cu NPs dependence on the oxidation state of Cu; perhaps this mechanism also takes place with the Cu ions but with a relatively low extent of ROS generation.[352] Higher intracellular ROS generation by Cu NPs is mainly due to its excellent ability to produce hydroxyl radical and catalyzing Fenton chemistry.[353] Moreover, sulfur radical formation by Cu (II) reduction of intracellular thiols has been also reported as an additional factor for ROS generation.[353] ROS generation results in oxidative damage of DNA as well as lipid peroxidation of membranes.[353] Apart from DNA oxidation, Cu NPs also impair its activity by directly binding with DNA domains. While in the case of Cu ions, protein activity is impaired by metal-catalyzed oxidation of amino acids residues, deactivation of iron−sulfur clusters, and displacement of essential cofactors from metalloenzymes.[353] Recently it was reported that Cu ions can increase bacterial cell wall permeability by binding with peptidoglycan LD-transpeptidase, a membrane-bound enzyme.[354] Metallic Cu or alloyed copper surfaces are well-known for the distinguishing phenomena of contact killing bacteria under dry conditions, but despite several investigations, the exact antibacterial mechanism of such bactericidal activities are not well explained.[341,347−349,355−357] Grass et al. proposed a series of steps for explaining the contact killing mechanism of Cu surfaces against the bacteria.[336] The first step is rapid dissolution of Cu ions from the Cu surface and accumulation on and within the bacterial cell membrane leading to membrane damage due to membrane depolarization. Furthermore, cellular components undergo oxidative degradation, and either genomic or plasmid DNA degradation takes place due to Cu induced ROS generation. Figure 17 shows the schematic illustrating contact killing mechanism of Cu surface, as explained by Grass et al.

As shown in Figure 17, the first step (a) is the Cu ion dissolution from the Cu surface leading to ion accumulation within the bacterial cell which results in membrane damage. In the second step (b), cell membrane rupturing takes place leading to membrane potential loss. In third step (c), ROS generation occurs, and in step 4 (d), DNA degradation takes place.

Copper-Based Antimicrobial Materials. Copper and copper-based materials have been used in various forms for antimicrobial application. Broadly, they can be classified into Cu and Cu-modified metallic substrates, Cu composites with glass and polymer, Cu-coated nonmetallic surfaces, and Cu-coated superhydrophobic surfaces.

Cu and Cu-modified metallic substrates find application mostly in hospitals as most of the frequently touched surfaces in the hospitals are made of stainless steel and are prone to contamination, so metal objects in hospitals are coated with Cu metal or its alloys that help in eliminating the microbial burden from 37 to 100%, owing to its contact killing phenomena. Commercially available objects in hospitals which are coated with copper and its alloys are available in the form of Cu alloy coated bed rails, brass tap handles, door push plates, doorknobs, copper-coated toilet seats, or

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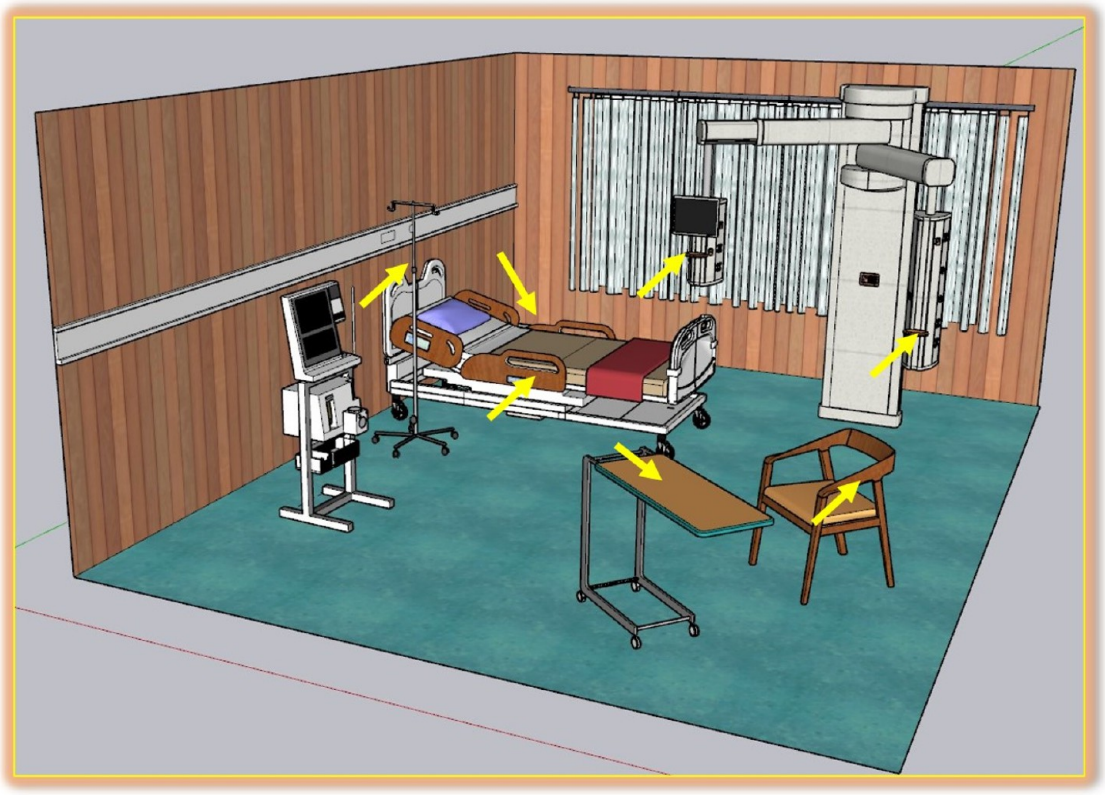

Figure 18. Representative image of frequently touched objects and their respective placements in the ICU. Graphic credit: Dr. P. Prabha (created using Sketchup pro 2020), used with permission.

computer accessories.[233,358−361] Figure 18 is the photographic image of a typical ICU room with the placement of various frequently touched objects.

A recent study has shown that modifying surfaces with Cu significantly reduced the rate of HAI and/or vancomycin-resistant enterococci or methicillin-resistant *S. aureus* (MRSA) colonization in ICU rooms.[361] A study conducted by Zerbib et al. reported that Cu coating on the surface of hand rails, door handles, and grab bars helps in lowering the infections that are spread by the hand-transmitted pathogens adenovirus and norovirus, mainly responsible for gastroenteritis and kerato-conjunctivitis.[362]

Cu and its alloys have been also found to be beneficial in the implants for biomedical application due to its antibacterial properties since implants are susceptible to the bacterial contaminations.[363,364] Cu is incorporated in implants either by developing new materials by alloying with copper or by doping the material surface with Cu using an ion implantation technique or coating with Cu. Most of the newer materials for implants are copper-based stainless steel or titanium (Ti). Copper-based stainless steel materials have been developed in the form of Cu alloyed with austenitic stainless steels such as 316L-Cu, 317L-Cu, 304-Cu, and 200-Cu as well as in the form of Cu alloyed with martensitic stainless steel such as 410s.[365−369] Cu-based stainless-steel implants are effective in preventing infection without perturbing the cell proliferation for a longer period. For instance, 317L-Cu implants reduced CFUs as well as minimized tissue inflammation.[370] Similar to Cu-based stainless steel, newer materials have been also developed using Cu-based Ti alloys for biomedical applications. Li et al. fabricated Cu-incorporated biomedical TiNi alloy via melting TiNi ingots and Cu in varying proportions at 1800 °C under an argon environment in an arc melting furnace.[364] This TiNiCu alloy decreased the cytotoxic effect of planktonic and adhered *S. aureus* as well as *E. coli* in human osteoblast cells and murine fibroblast cells. Ti−Cu alloys used as dental implant material prevented *S. mutans* and *Porphyromonas gingivalis* biofilm growth. Although Cu-based stainless steel and Ti materials show promising results for biomedical applications, fabricating Cu-surfaced materials is much simpler for rendering the surfaces antibacterial.

Cu-surfaced materials are fabricated via a surface doping technique achieved by implanting active ions, e.g., Cu and Ag, also known as "antibacterial metal dopants" for providing antibacterial properties to the surfaces.[363] Cu implantation is normally achieved through metal vacuum source arc, and Cu implantation dose is varied. Dan et al. reported 99.9% killing rate of *E. coli* when the surface of AISI 420 stainless steel underwent Cu implantation illustrating its excellent anti-bacterial property.[371] This material had an efficacy of 40−60% against *S. aureus* bacteria, which further increased to 100% on increasing Cu dosage. The antibacterial effect of Cu implantation biomedical application was also observed in a varying range of materials such as 317L stainless steel, Ti−Al−Nb alloy, and pure Ti.[372] It was found that at a particular dose of ion the actual concentration of Cu on the surface depended on the nature of the substrate. Consequently, the results indicated that conditions during ion implantation can control the chemical state of Cu at the surface of the substrate.[373] For example, the presence of oxygen (O_2−Cu-PIII) or water vapor (H_2O−Cu−PIII) during plasma-immersion implantation (PIII) in TiO_2 formed phases that were rich in Cu or Cu-oxide.

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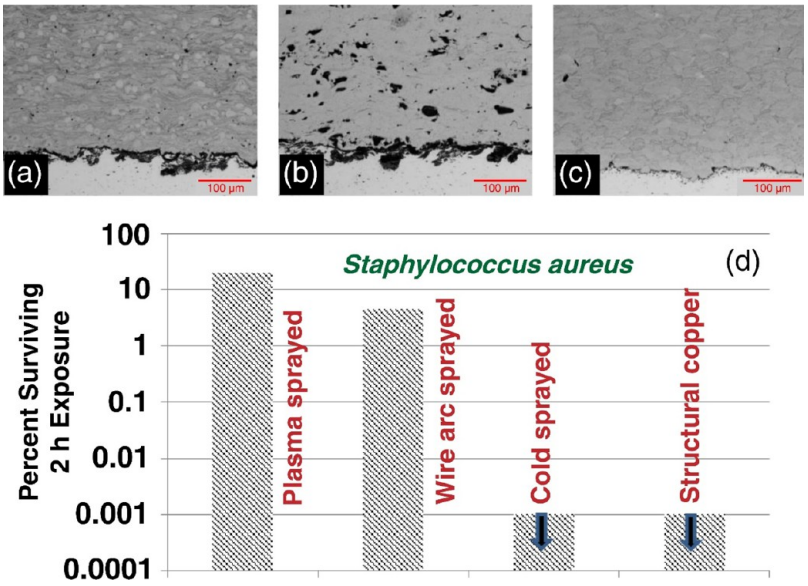

Figure 19. Deposited copper cross sections. (a) Plasma, (b) wire arc, (c) cold spray, and (d) percent of MRSA surviving after a 2 h exposure to copper surfaces. Reproduced with permission from ref 375. Copyright 2019 MDPI, Basel, Switzerland.

Copper-Based Thin-Film Antimicrobial Coatings. The metallic surface can be rendered antibacterial by depositing Cu thin films on the metallic surface. Numerous coating techniques have been employed by the researchers to make the surface antibacterial. Wang et al. employed magnetron sputtering to coat Cu on the Ta surface, where it was observed that increasing deposition time increased thickness of coating with increasing surface roughness.[374] Cu-based Ta surface was effective against *S. aureus* and *E. coli*.

In a separate study for commercial applications, different metal spray techniques such as wire arc spray, plasma spray, and cold spray were used to fabricate Cu coatings that were 0.3 mm thick.[375] Figure 19a–c shows the cross-sectional image of the Cu deposited over stainless steel using various techniques depicting clear difference of deposition techniques on the microstructure of Cu coating. Wire arc and plasma sprays are high-temperature processes (1500–2000 °C), whereas cold spray is a relatively low temperature process (1500–2000 °C). Cold spray assisted Cu coating showed better antibacterial efficacy against MRSA compared to coatings based on other two techniques, primarily due to dislocation formation that promoted beneficial ion diffusion through the metallic coating responsible for accelerated bacterial killing. Figure 19d shows the survival percent of MRSA with the exposure time of 2 h on copper surfaces. In another study, it has been also shown that implants coated with Cu can be promising materials for *in vivo* applications. This was elucidated from a study where copper galvanically coated on Ti6Al4 V nails was found effective in fixing a tibia fracture in rabbits by increasing the callus index in animals, implying that Cu ions can stimulate bone formation.[376] Together with the usage of pure Cu for coating, codeposition of Cu along with other metals have been also employed to fabricate antimicrobial coating. Ti–Cu nitride films were fabricated on Ti substrates via plasma spray of Ti subsequently followed by physical vapor deposition of TiCuN.[377] These surfaces exhibited higher antibacterial efficacy against S.*epidermidis*. Moreover, these coatings also inhibited osteoblasts by inhibiting bacterial colonization, but these coatings still require optimum design criteria to control the release of Cu ions for higher antibacterial efficacy. Electroplating is yet another technique is used to develop a Cu antibacterial coating on stainless steel.[378] In this technique, a Cu–Ag alloy composed of ∼60% Cu and ∼40% Ag is deposited on stainless steel. This coating demonstrated exceptional antibacterial properties against *S. aureus* and *E. coli* over pure Cu or Ag due to localized and selective dissolution of Cu over Ag in chloride environment owing to the galvanic coupling of Cu with Ag. Apart from being an excellent candidate for antimicrobial coatings, antiviral properties of the copper have also been well documented in the literature. Hodek et al. prepared an effective protective hybrid coating comprising of copper, silver and zinc cations against human immunodeficiency virus type 1 (HIV-1), dengue virus, influenza, herpes simplex virus and coxsackievirus. This hybrid coating was prepared by radical polymerization via a sol–gel method which was applied on poly(methyl methacrylate) plate wells or glass slides. Several viruses were added to the coated as well as uncoated slides and plates that were incubated followed by titer determination.[5] Ditta et al. found that glass coated with CuO and CuO/TiO_2 hybrid by atmospheric chemical vapor deposition (Ap-CVD) was effective in inactivating enteric virus, which suggested that copper toxicity and photocatalysis worked synergistically in deactivating bacteriophage T4.[379]

Antimicrobial Properties of Copper-Based Nanostructures. In the past few years, Cu has been also employed in various nanostructure forms for modifying the substrate surface to control the cell attachment for various tissue engineering applications. A study carried out by Rosenbaum et al. found that depositing Cu cubes on the TiO_2 modified Ti substrate effectively prevented *E. coli* and *S. aureus* bacteria from adhering to the surface.[380] There have been a few reports where Cu NPs were incorporated in hydrogel and polymers to prevent aggregation of NPs for modifying metallic surfaces. Cu NPs were immobilized on stainless-steel substrates consisting of a poly(ethylene glycol diacrylate) (PEGDA) hydrogel by an electrochemical polymerization process that showed superior efficacy against *E. coli* and *S. aureus*[381] In a separate study, Cu(II) ions were incorporated in a polydopamine (PDA)

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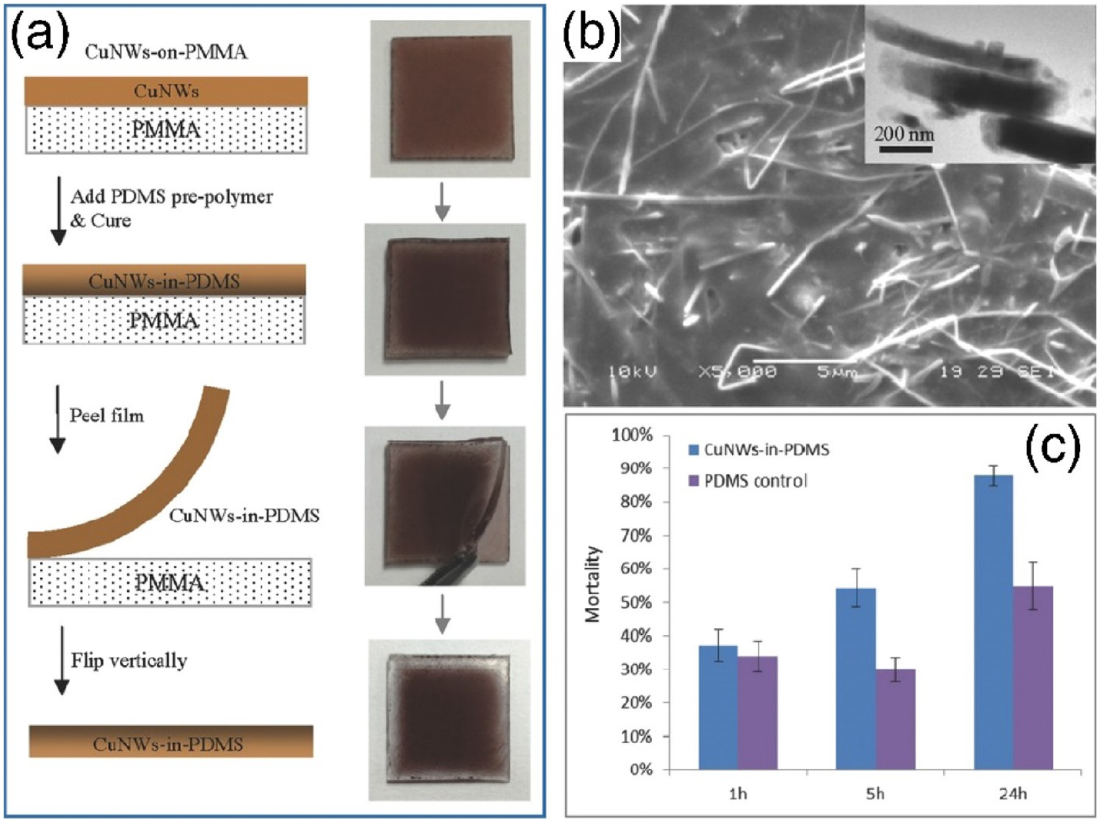

Figure 20. Fabrication and antibacterial activities of the CuNWs-in-PDMS film. (a) Schematic illustration and photographs for the fabrication of the CuNWs-in-PDMS film. (b) SEM image of the peeled CuNWs-in-PDMS film at the surface originally facing the PMMA slide; scale bar is 5 μm. The inset is a TEM image of a thin cross section of the CuNWs-in-PDMS film obtained by perpendicular sectioning using a cryo-ultramicrotome. (c) Mortality of *E. coli* cells after incubation in PBS buffer for 1, 5, and 24 h with the CuNWs-in-PDMS film and a PDMS slide as a control. Reproduced with permission from ref 387. Copyright 2015 John Wiley and Sons.

coating on Ti substrates that resulted in a killing rate of 85% against *S. aureus* and *E. coli*.[382]

Fujimori et al. investigated the efficacy of CuI NPs against H1N1 influenza virus of swine flu by titration essay and found that reduction in virus titer was dose-dependent when the virus was incubated with CuI NPs. They rationalized virus inactivation to the hemagglutinin and neuraminidase degradation by CuI. Furthermore, this study envisioned the use of CuI NPs as a viral protective coating material in filters, face masks, and other personal protective equipment in healthcare settings.[383]

Apart from the antimicrobial properties of copper via contact killing of bacteria to be used in hospitals, there have been only a few reports on the use of copper as an antiviral surface for use in hospital settings. Sundberg et al. deposited an effective nanocopper coating on aluminum substrate against influenza A virus by cold spraying technique. Superior efficacy of this coating against influenza virus A resulted due to enhanced ionic diffusion owing to increased grain boundary evolution upon work hardening during the cold spraying process.[383]

The antiviral property of copper in the form of copper oxide has been investigated in various forms such as latex, fibers, filter matrix, and other polymeric materials. Filters made from copper oxide were effective in neutralizing HIV-1 in the medium as well as breast milk. Moreover, these filters effectively reduced several DNA and RNA viral titers along with other viruses such as influenza A virus, yellow fever virus, respiratory syncytial virus, cytomegalovirus, and yellow fever virus.[47] Borko et al. developed copper-containing latex gloves which decreased the infection caused by HIV.[384]

Antimicrobial Properties of Copper Composites with Glass and Polymer. Besides Cu coating on metallic substrates in the form of NPs, thin films, and alloys, fabrication of free-standing thin films of Cu-containing composites on non-metallic substrates has been also investigated. Cu-containing composite films are more durable than their counterpart due to the larger reservoir of an antimicrobial agent provided by copper. Polymers are considered to be the most suitable matrix for incorporating Cu NPs or Cu ions due to their excellent solubility. Subsequently, the composite solution can be easily cast as thin films or free-standing thin films on substrates. Palza et al. studied the antibacterial effects of the polymer composites by embedding Cu particles of 45 μm and 10 nm in a polymer matrix of polypropylene (PP), high-density polythene (HDPE), and polyamide 6.[385] Excellent antimicrobial efficacy of such composites was found toward *S. aureus* bacteria that varied depending on the size of the Cu particles, duration, and the nature of polymeric matrix (hydrophobic/hydrophilic and crystallinity). In another study, composites of Cu-embedded water-insoluble polymers such as polyvinyl chloride (PVC), polyvinyl methyl ketone (PVMK), and polyvinylidene fluoride (PVDF) were spin-coated on inert substrates, and their antifungal efficacy was investigated.[386] Cu-PVDF composite exhibited a lower antifungal efficacy over that of former composites due to the slow rate of Cu release from PVDF composite.

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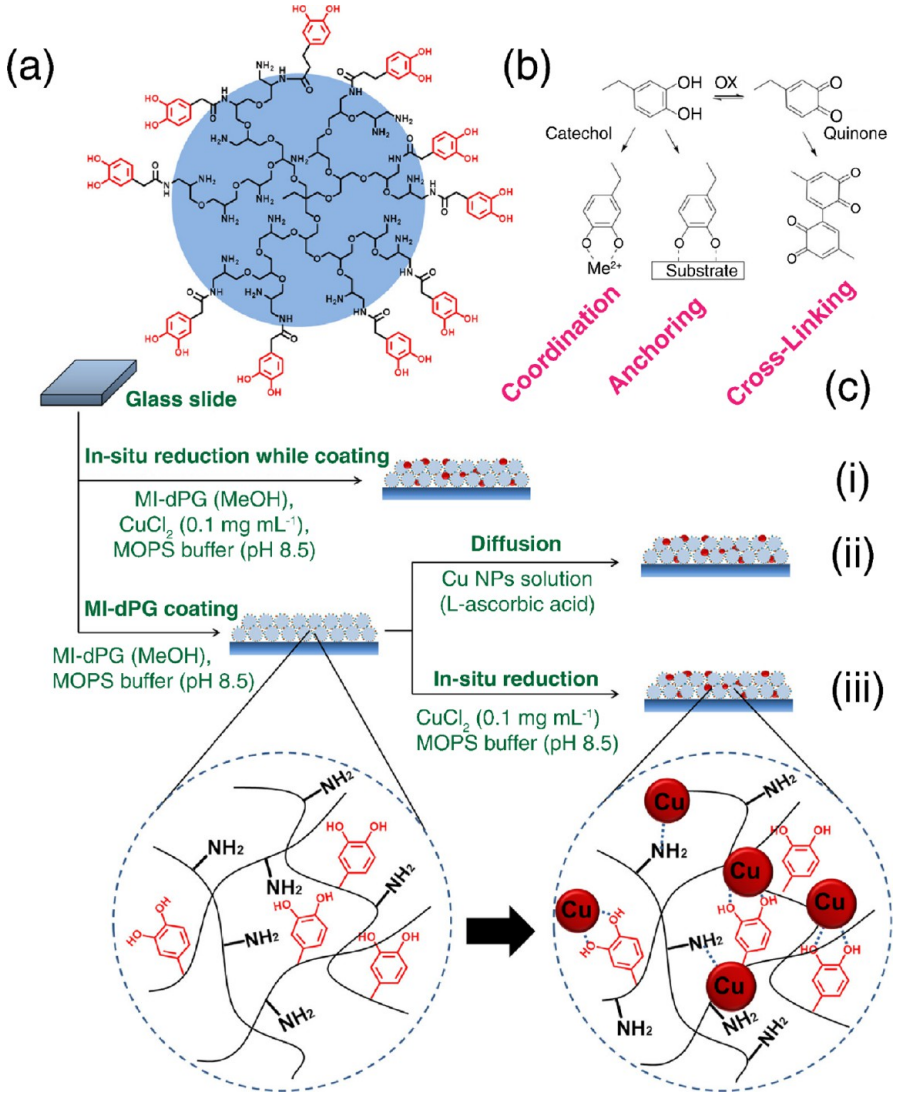

Figure 21. Chemical structure of MI-dPG. (a) Mechanism of catechol anchoring and cross-linking. (b) Preparation of Cu NP-incorporated MI-dPG surface coatings through three different ways. (c) All substrates were prepared on 1.0 × 1.0 × 0.1 cm^3 samples of glass slides. Reproduced with permission from ref 396. Copyright 2017 American Chemical Society.

Jiang et al. developed PDMS-encapsulated Cu nanowires (NW) as a marine antifouling coating to protect marine vessels from seawater (Figure 20).[387] Cu NW-PDMS composite was fabricated by growing a network of Cu NW by a disproportionation reaction on a poly(methyl methacrylate) (PMMA) substrate, subsequently followed by PDMS polymer addition and curing. Figure 21a shows the incorporation of Cu NWs in the PDMS matrix. It was found that the PDMS matrix helped slow the rate of corrosion of the Cu NW in seawater for more than 50 days. SEM images in Figure 21b illustrate the peeling-off of the Cu NWs in the PDMS films at the surface which faces the PMMA slide. When the composite film was incubated in PBS solution with *E. coli* for 1 h, no such antimicrobial effect was observed (Figure 21c). However, as the release of Cu ions progressed with the time, the antimicrobial effect was observed after 5 h, and by 24 h, nearly 90% of the bacterial cells were destroyed in comparison to 60% bacterial cell killing with the control PDMS surface. A pilot study conducted at an adult ICU for 9 weeks using Cu particles embedded in a methyl methacrylate composite reduced bacterial burden by over 99.9%.[388] Promising results were obtained when the same formulation was utilized with high-touch surfaces such as an over-bed table, bed rails, and IV poles in the hospital environment. Although a prominent reduction in the microbial load was observed, the fungi/yeast burden remained unaltered. Composites of Cu-doped nanolaponite deposited over a PDA-coated polybutylene succinate scaffold were found useful in reducing the bacterial load of *S. aureus* and *E. coli* by 90.7 and 92.3% respectively, thus making it a suitable candidate for orthopedic applications.[389]

Another class of Cu composite employing glass-ceramics or bioactive glass as the matrix have been investigated for antimicrobial biomedical applications. Bioactive glasses have been already extensively used in the field of biomaterial driven regenerative medicine.[390] They are primarily composed of silicon dioxide along with the varying composition of compounds such as oxides of calcium, sodium, and phosphorus depending on the response of body for clinical applications (soft or hard tissue generation).[390,391] Briefly, bioactive glasses are manufactured by sol−gel or melt quenching process followed by Cu precursor addition. For example, a glass-ceramic composite having the composition of $60SiO_2{\cdot}(32 -$

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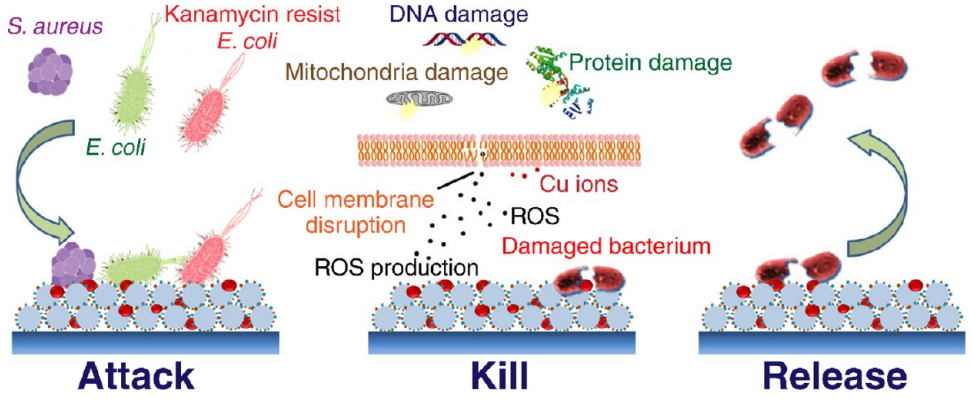

Figure 22. Schematic illustration of the contact killing of bacteria on a Cu NP-incorporated MI-dPG surface coating via the "Attract−Kill−Release" route. Reproduced with permission from ref 396. Copyright 2017 American Chemical Society.

Table 4. Cidal Concentration of Different Types of Organisms with Respect to Various Antimicrobial Materials

material	type of organism	minimum inhibitory concentration (MIC)	minimum bactericidal concentration (MBC)	ref
Ag−Fe alloys with graphene-based cellular monolith	*E. coli*	80 ppm	50 ppm	44
Ag−Fe alloys with graphene-based cellular monolith	*S. aureus*	100 ppm	80 ppm	44
graphene oxide−silver NP nanohybrid	*E. coli*	64 μg/mL	NA	311
graphene oxide−silver NP nanohybrid	*P. aeruginosa*	64 μg/mL	NA	311
graphene oxide−silver NP nanohybrid	*S. aureus*	32 μg/mL	NA	311
graphene oxide−silver NP nanohybrid	*C. albicans*	32 μg/mL	NA	311
Ag@Zn-BIF	*E. coli* and *S. aureus*	30−50 μg/mL	NA	314
titanium dioxide and zinc oxide NPs supported in 4A zeolite	*E. coli*	1 ± 0.01	2 ± 0.01	400
	S. aureus	2 ± 0.01	3 ± 0.01	
	Pseudomonas fluorescens	1 ± 0.01	2 ± 0.01	
	L. monocytogenes	2 ± 0.01	3 ± 0.01	
5% Cu-alloyed Ti	*S. mutans*	800 μL of ~10^5 (or ~10^7) CFU/mL	NA	401
1, 4, 7, and 10% Cu-alloyed TiNi	*S. aureus* and *E. coli*	~10^6 CFU/mL bacteria	NA	364
Cu-ion-implanted 420 stainless steel	*E. coli* and *S. aureus*	1 mL of ~10^5 CFU/mL	NA	371
Cu-ion-implanted Ti	*S. epidermidis*	200 μL of ~10^6 CFU/mL	NA	373
Cu-coated Ta	*E. coli* and *S. aureus*	1 mL of ~10^6 CFU/mL	NA	374
TiCuN-coated Ti	*S. epidermis*	1 mL of ~10^3 CFU/mL	NA	402
Cu−Ag-coated 316 and 316L stainless steel	*S. aureus* and *E. coli*	2 mL of ~10^6 CFU/mL	NA	378
Cu-coated PMMA	cyanobacteria	1 mL 10^9 CFU/mL	NA	403
Cu NP/PEGDA hydrogel-coated stainless steel	*S. aureus* and *E. coli*	10^7 CFU/mL	NA	381
Cu NP-coated polyester fabric	*S. aureus*	200 μL	NA	404

x)CaO.8P_2O_5·xCuO with a CuO concentration of 0.5 mol % was prepared by a sol−gel method and was found to inhibit *S. aureus* and *P. aeruginosa*.[391] Ryan et al. functionalized a collagen scaffold with Cu bioactive glass composites for the treatment of osteomyelitis.[392] Gross et al. incorporated a Cu-glass ceramic powder in commercial paints for adding antimicrobial properties to the paints.[393]

Copper-Incorporated Nonmetallic Antimicrobial Surfaces. Until now we have seen antimicrobial properties of Cu and Cu-modified metallic substrates and composites in the health care setting and biomedical applications, but fabrication has not been examined for antimicrobial products for frequently touched objects in the healthcare setting such as syringe pumps, ventilators, and touch screens as well as biomedical devices, e.g., nonmetal prosthetics, catheters, and breast implants. There have been only a few investigations on antimicrobial Cu coatings endowing the surfaces of elastomers, polymers, and glass. Since most of the fabrication techniques for copper coatings utilize high-temperature processes such as wire or plasma arc or magnetron sputtering which exceed the melting point temperature (T_m) of the polymers, it becomes very difficult to deposit thin films of copper on polymeric substrates. Moreover, the nonconductive nature of polymeric substrates also limits the widely used electroplating technique for a Cu thin film coating on such substrates. However, the recent development of low-temperature techniques such as atmospheric pressure plasma deposition and spray deposition techniques have enabled the deposition of metallic copper on nonmetallic substrates such as polymers and elastomers.[394,395] Recently, Wu et al. developed a self-sterilized, rugged antimicrobial coating over ultra-high-molecular-weight polythene (UHMWPE) using an aerosol-assisted low-temperature (170 °C) chemical vapor deposition technique.[394] The antimicrobial coating reduced the bacterial load of *S. aureus* and *E. coli* by 99.999% within just 15 min; moreover, its excellent abrasion resistance property and mechanical strength make this coating a promising candidate for prosthetic joint applications. In another study, a nonthermal air-operated direct

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current plasma jet technique was employed for depositing Cu over acrylonitrile butadiene styrene (ABS) as an implant material at room temperature.[395] The highest antimicrobial efficacy of 93% was achieved against *S. aureus* using modified ABS. To tackle the problem of the controlled rate of Cu ion release from entrapped Cu NPs for higher antibacterial efficacy, Li et al. fabricated Cu-embedded mussel-inspired dendritic polyglycerol (MI-dPG) over a glass slide.[396]

Figure 21a,b illustrates the chemical structure of catechol and MI-dPG anchoring and their cross-linking mechanism, while Figure 21c depicts the three different routes for Cu incorporation. It was found that these coatings were highly stable in bacterial suspension, and CFU were reduced by 99.99% for *S. aureus* and *E. coli* bacteria. Chitosan is another polymer that is used to immobilize Cu ions or NPs by Cu chelation with the amino and hydroxyl groups present in chitosan. Due to the chelation property of chitosan, Gosau et al. fabricated Cu-embedded chitosan coating on silicone as an antimicrobial coating against *S. epidermis*.[397] The schematic illustration of the contact killing of bacteria on a Cu NP-incorporated MI-dPG surface coating via the "attract−kill−release" route is shown in Figure 22. Additionally, no cytotoxicity was observed against mammalian cells, but the main challenges with such a polymeric coating is the limited immobilization of Cu ions via chelation with polymer functional groups. To improve the Cu loading, SiO_2 NPs were deposited on chitosan covalently dispersed over PVDF films which exhibited about 100% efficacy against *S. aureus*.[398] On similar grounds, Mitra et al. prepared a chitosan coating via covalent grafting of acrylated quaternized chitosan (ACQS) and EDTA on PVDF or stainless steel, in which EDTA worked as a chelating agent and increased number of complexation sites for Cu ions.[399] This coating killed ∼96% *S. aureus*, while exceptionally no CFU were observed with *P. aeruginosa*, one of the most virulent and hardest to kill bacteria. The increased rate of Cu release from the coating was proposed as the reason for its superior efficacy against *P. aeruginosa*.

Furthermore, the cidal concentrations play a major role in controlling the microbial spread. We have listed out the cidal concentrations of the antimicrobial materials for different types of organisms in Table 4.

Copper-Based Antimicrobial Fabric Coatings. Cu NPs incorporated into superhydrophobic surfaces have been widely used for antimicrobial applications. Cu NPs play a dual role of antimicrobial agent as well as also provide additional surface roughness to improve the superhydrophobicity of the surfaces. The superhydrophobicity of these surfaces has encouraged their usage as antimicrobial fabric coatings. Suryaprabha et al. fabricated superhydrophobic cotton fabric coated with Cu by reducing copper acetate followed by immersion of fabric in stearic acid.[405] This Cu-coated fabric showed more inhibition against Gram-negative and Gram-positive bacteria compared to that of nonhydrophobic Cu-coated fabric. Interestingly, superhydrophobic fabric still showed excellent hydrophobicity after abrasion with sandpaper followed by washing with detergent and water.[405] Hong et al. deposited Cu and Ag NPs of average diameters of ∼788 and 215 nm, respectively, on the PDA-coated polyester fabric. The Cu-deposited fabric exhibited >99% efficacy against *S. aureus*.[404] Subsequently, another study reported that superhydrophobic cotton fabric incorporated with SiO_2 sol doped with Cu NPs showed increased antibacterial efficacy against Gram-positive bacteria.[406] Xu et al. reported Cu NPs coated on cotton fabric as antimicrobial agent and used thioglycolic acid (TGA) as binder and citric acid as protective reagent. The double stabilization action of TGA and citric acid helped the uniform immobilization of NPs, which resulted in excellent antibacterial efficacy against *S. aureus* and *E. coli* and improved launderability of fabric.[407] Surface-initiated grafting polymer brushes have been used to bridge copper NPs on cotton fabrics and substrates to improve their durability. These antibacterial coatings attributed to strong chemical bonds between Cu NPs and fabric. Fabric coated using Cu NPs showed excellent antibacterial activity against *S. aureus* and *E. coli* after 30 cycles of washing.[408] Borkow et al. developed a novel platform technology where copper oxide was impregnated into the polymeric fibers or cotton fibers, rendering fibers with potential broad-spectrum antiviral, antibacterial, antifungal, and antimite properties. This technology enabled the mass production of nonwoven and woven fabrics with no alteration requirement for industrial procedures. Moreover, this technology opened a way to produce filters and antiviral gloves (for HIV-1 and other viruses), antibacterial self-sterilizing fabrics, antifungal socks, antimite mattress covers, and gauzes.[409] Recently, Eremenko et al. used a wet chemical method to prepare Cu NPs and deposit them on cotton woven fabric using a pad-dry−cure method. It was found that the finished fabric resulted in significant antibacterial efficacy against *S. aureus* in both the quantitative and qualitative tests. Additionally, it was also found that developed fabric was durable and exhibited withstanding capability even after 25 wash cycles.[410]

■ SAFETY CONCERNS AND MITIGATIONS

In the biomedical era, polymeric (synthetic and biopolymers) and nanomaterials including metal and metal oxide are gaining significant attention and dramatic progress due to their small size, large surface area, flexible surface modifications, unique biocidal delivery properties, loading capability, biodegradability, enhanced surface charge, self-assembly, smart release, and inherent antimicrobial properties.[27,388,411−417] In order to enhance their potential in specific biomedical field, their physicochemical properties and structural as well as biological characteristics need to be enhanced through doping, size control, and surface modifications.[27,60,418] Recently, few reports have analyzed the toxicity profile of antimicrobial polymers and nanomaterials.[413,419−422] Hence, during the design of experiments, while preserving the biomedical functions of these polymeric or nanomaterials, toxicological evaluation should also be taken into consideration through preclinical and clinical tests of both *in vivo* and *in vitro*.[411,412] The materials need to pass through the safety aspects to combat the nanotoxicological affect before their application. For antimicrobial coatings in healthcare settings, safety is one of the predominant deciding factors to "graduate" the materials to the next level of use.[413] Compromising on screening of the materials, especially nanomaterials and polymer NPs, poses risks and dangers to human health as well as to the total environment. "Nanosafety" is to be ensured while designing or redesigning the biocompatible, safe, and optimized nano or polymer materials in the desired field of biomedical applications. The "safer-by-design" term has to be ensured during the design of antibacterial, antiviral polymeric and nanomaterials to avoid their adverse effects on human health.[412]

In order to elevate the antibacterial and antiviral coatings based on polymers and nanomaterials, the uncertainty

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evidenced in the evaluation of the nanotoxicology profile of antimicrobial materials needs immediate attention. To this end, certain key criteria such as high antimicrobial efficacy with dosage optimization, selectivity on pathogenic micro-organisms, low cytotoxicity, response based on target, and clinical trials should be comprehensively addressed. Recently, the smart entry of artificial intelligence (AI) based on machine learning algorithms has shown the path for a simplified approach on choosing antimicrobial materials based on their physicochemical, mechanical, and biological based comparisons. Hence, we are not far from realizing the immense potential of AI in healthcare settings, especially in designing the safer materials as it enables ease in grading of materials based on their nanotoxicological profiles.[423]

Finally, no matter how smart or intelligent the material is, it will not be widely used if it fails on the safety aspects, especially in healthcare-related applications, so optimizing the products to render them safe for applications related to human health is of prime importance. Ensuring low or zero toxicity of NPs or polymeric composites when employing them as antimicrobial coatings or materials is one of the major challenging tasks.[27] Many reports comprehensively have presented the nanotoxicological evaluation data of antimicrobial nanomaterials and polymers and support the same.[419,424,425] In addition to the development of newer and more effective materials, future work in this area is also expected to focus on the control and evaluation of the toxicity of nanomaterials and polymers.

CONCLUSIONS AND OUTLOOK

Over the past 100 years, the world has faced pandemic-like situations several times, and due to the emergence of new pathogens, there has always been a need for new antimicrobial therapies. In addition to drugs, a reliable way to prevent the spread of infections has led to the development of antimicrobial materials for application to surfaces. The demand for antimicrobial materials has further increased the potential market mainly in the healthcare sectors. Despite a large number of publications describing antimicrobial materials and their applications in various sectors, there are many challenges for the advancement of antimicrobial materials toward their commercialization. To overcome these challenges and take forward antimicrobial materials and coatings to the level of industrial and commercial applications, there is a need to thoroughly balance efficacy, toxicity, and cost which will drive future innovation in this area. Through bridging of these gaps, progress will inevitably be seen in the adaptation of smart antimicrobial materials or surfaces or coatings in healthcare settings.

The advantages of antibacterial and antiviral polymers, metals, and oxides in various surface applications are discussed in this Review. Antibacterial and antiviral materials or surfaces have the potential for controlling the healthcare-related infections; thereby, the spread of pandemics like COVID-19 can be controlled to the extent possible. Two important mechanisms, e.g., contact killing and surface repelling, were discussed in detail. However, more detailed and systematic pursuance of antimicrobial mechanisms with antimicrobial agents (polymers, nanomaterials, or polymeric nanocomposites) needs to be explored. This will lead to an in-depth understanding of the action of the effective killing of bacteria (the integrity of subcellular structures collapse, cell membrane disrupter, protein synthesis inhibition, and DNA interaction) by the selective antibacterial materials. To provide a comprehensive chemical insight into the existing or newly developed antimicrobial agents, it is essential to understand and fine-tune their macroscopic/microscopic factors such as physicochemical stability, structural characteristics, surface interactions and their compatibility, solvent selection during the synthesis to protect the cell degradability, and stability against external conditions, e.g. heat and light. A chemical database containing optimized experimental conditions and its antimicrobial correlation needs to be created to design and synthesize antibacterial or antiviral materials. The translational research effort is the "need of the hour" toward exploring new avenues for advanced antimicrobial materials.

The major fundamental challenges are the development of cost-effective and environmentally friendly or compatible antibacterial/antiviral polymers or a combination of polymers with nanomaterials or metals. However, the reusability aspects of such antimicrobial materials have not yet been studied in detail and require immediate attention. Often, the reported studies emphasize on utilizing the potential of bio-based or biodegradable polymers as a replacement for synthetic polymers, which pose greater health hazards if the dosage is not controlled while preparing the antimicrobial and antiviral materials. However, metals such as silver and copper have displayed antimicrobial properties, but the lack of an established mechanism for their action is a great barrier in the metal-based antimicrobial material's research. As far as the antimicrobial properties of TiO_2 are concerned, it has failed the litmus test such as unified mechanism approach. Also, the two mechanisms of protection enabled by antimicrobial polymers or combined metallic or oxide based antimicrobial materials on various substrates need to be discussed and should bring new knowledge to promote industrial scale-up. One more important thing which needs further attention is the use of same antimicrobial materials for different types of emerging pathogens, as it allows their use as broad-spectrum antibacterial agents. A control of leaching of these antimicrobial polymers or other materials when applied over substrates, e.g., glass, wood, paper, and fabrics, has to be properly studied with a well-developed protocol. The lack of wide-scale applications of emerging antimicrobial materials or polymers is due to the lack of data based on the nanotoxicological evaluation criteria. The landscape of healthcare and biomedical research is gradually changing with the entry of AI. It would be good to adopt this technology which consists of machine-learning models trained on the data from the literature to quickly screen for antimicrobial polymers or nanomaterials with respect to its chemical and biological toxicity profiles and clinical trials, while developing safer medical-device-based smart coatings.

Despite the promising outlook for functional polymers, biopolymers, and nanomaterials in tackling the microbial burdens, critical challenges still remain. These challenges in the biomedical applications could be overcome by adopting biomimetic or bioinspired test methods such as smart functional coatings, responsive coatings, or design methods, namely, 3D printing, to further solve the microbial infections. The *in vivo* test methods and specific clinical trials have an impact on screening of antimicrobial materials in addition to *in vitro* test methods. This will enhance their potential use not just qualitatively but also quantitatively in realistic and challenging heterogeneous environmental conditions. Hence, *in vivo* and *in vitro* evaluations aimed at assessing the toxicity of these materials is the necessary for their bright future in the

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healthcare field. Hence, it can be concluded that with the concerted effort via fulfilling the fundamental requirement and industrial-scale development, the antibacterial and antiviral materials or coatings field can achieve greater heights in the coming years to fight against the harmful pathogens and save millions of people from getting infected.

AUTHOR INFORMATION

Corresponding Authors

Raju Kumar Gupta − *Department of Chemical Engineering and Center for Environmental Science and Engineering, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208016, India;* orcid.org/0000-0002-5537-8057; Email: guptark@iitk.ac.in

Anand Singh − *Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208016, India;* orcid.org/0000-0001-9703-6306; Email: anands@iitk.ac.in

Authors

Bhuvaneshwari Balasubramaniam − *Department of Chemical Engineering, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208016, India;* orcid.org/0000-0001-6883-5731

Prateek − *Department of Chemical Engineering, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208016, India*

Sudhir Ranjan − *Department of Chemical Engineering, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208016, India*

Mohit Saraf − *Department of Chemical Engineering, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208016, India;* orcid.org/0000-0002-2566-5581

Prasenjit Kar − *Department of Chemical Engineering, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208016, India*

Surya Pratap Singh − *Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur, Uttar Pradesh 208016, India*

Vijay Kumar Thakur − *Biorefining and Advanced Materials Research Center, Scotland's Rural College (SRUC), Edinburgh EH9 3JG, United Kingdom;* orcid.org/0000-0002-0790-2264

Complete contact information is available at: https://pubs.acs.org/10.1021/acsptsci.0c00174

Author Contributions

⊥B.B. and Prateek contributed equally to this work.

Notes

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