Antimicrobial polymeric composites for high-touch surfaces in healthcare applications

Minghui Liu[1,2], Lukas Bauman[1,2],
Christiane Lourenco Nogueira[1], Marc G. Aucoin[1],
William A. Anderson[1] and Boxin Zhao[1,2]

Abstract

Antimicrobial polymer composites have long been utilized in the healthcare field as part of the first line of defense. These composites are desirable in that they pose a minimal risk of developing contagions with antibiotic resistance. For this reason, the field of antimicrobial composites has seen steady growth over recent years and is becoming increasingly important during the current COVID-19 pandemic. In this article, we first review the need of the antimicrobial polymers in high tough surfaces, the antimicrobial mechanism, and then the recent advances in the development of antimicrobial polymer composite including the utilization of intrinsic antimicrobial polymers, the addition of antimicrobial additives, and new exploration of surface patterning. While there are many established and developing methods of imbuing a material with antimicrobial activity, there currently is no standard quantification method for these properties leading to difficulty comparing the efficacy of these materials within the literature. A discussion of the common antimicrobial characterization methods is provided along with highlights on the need of a standardized quantification of antiviral and antibacterial properties in testing to allow ease of comparison between generated libraries and to facilitate proper screening. We also discuss and comment on the current trends of the development of antimicrobial polymer composites with long-lasting and specific antimicrobial activities, nontoxic properties, and environmental friendliness against a broad-spectrum of microbes.

Addresses
[1] Department of Chemical Engineering
[2] Waterloo Institute for Nanotechnology & Institute for Polymer Research, University of Waterloo, 200 University Avenue West, Waterloo, Ontario N2L 3G1, Canada

Corresponding authors: Zhao, Boxin (zhaob@uwaterloo.ca); Aucoin, Marc G (marc.aucoin@uwaterloo.ca); Anderson, William A (wanderson@uwaterloo.ca)

Introduction

Healthcare associated infections (HAI) have seen a significant increase along with the development of modern clinical treatments, including central line-associated bloodstream infections, catheter-associated urinary tract infections, and ventilator-associated pneumonia as well as various pathogens transferred through high touch surfaces (HTS) such as (methicillin-resistant) *Staphylococcus aureus*, vancomycin-resistant enterococci, *Clostridium difficile*, multidrug resistant Gram-negative bacilli, norovirus, coronavirus and *Candida* species [1]. *HAI Hospital Prevalence Survey shows that* approximately one out of 31 hospital patients has at least one HAI any day, leading to an estimated 72,000 deaths due to the 687,000 HAIs in U.S. acute care hospitals in 2015 [2]. Although, bacteria and fungi are considered the primary threat for nosocomial infections, viral infections make up an estimated 60% of all infections [3,4]. The World Health Organization (WHO) has stated that multi-drug resistant pathogens will cause 10 million deaths worldwide each year by 2050 [5] and 100 trillion USD in associated cost [6]. To prevent HAIs while minimizing the possibility of drug resistance, the development of novel antimicrobial materials has drawn significant research attention. For this review, "antimicrobial" and "biocidal" will include action against viruses, bacteria, and fungi. Antimicrobial materials will therefore inhibit the growth, reduce the viability, or outright kill pathogens to reduce the occurrence of HAIs.

While antimicrobial activity includes all forms of biocidal activity, it should be noted that most studies of antimicrobial activity focus exclusively on bactericidal activity. Although many of the compounds and molecules that render materials bactericidal are also effective against other infectious agents, material testing for virucidal or fungicidal properties is less common with methodologies being ill-defined. With threats such as

SARS-CoV-2 and *Candida auris*, consideration of the different mechanisms that can lead to biocidal activity is still needed. Furthermore, while the source and type of microbial agent that leads to HAI can vary significantly, their ability to survive on surfaces plays a key role in increasing the probability of an adverse outcome. For bacteria, the formation of biofilms plays a significant role in the contamination of surfaces. Biofilm formation provides a dense gathering of microbes, which expedites the antibiotic-resistant genes to spread throughout all cells within the biofilm due to the horizontal gene transfer. Data from the National Institutes of Health (NIH) have shown that 80% of pathogenic bacterial infections during healthcare treatment are related to biofilms [7].

Unlike the antimicrobial activity of metal surfaces, notably copper and silver, which has been known for several centuries, the first polymeric materials with this property, 2-methacryloxytroponone polymers and co-polymers, were first studied in 1965 [8]. In the 1970s, investigations of salicylic acid-based polymers and polymers with quaternary ammonium groups were performed for their antimicrobial activity. This modest beginning contrasts with the current state of the art, where a comprehensive analysis of the Google Patent Search database by Julieta et al. found more than 27,845 patents filed since 2013 relating to antimicrobial polymers [9]. Alas, the variety of infectious agents and the near-limitless ability to create novel materials make this a combinatorial problem that is soon becoming, if not already, too hard to navigate without standardization. This review aims to highlight the most recent advances in antimicrobial polymeric materials, the basis of their design and how they are tested, with a focus on the use of such materials in solid—air interfaces (i.e. high touch surfaces) in the healthcare environment.

High-touch surfaces and the use of antimicrobial polymer composites

In the hospital setting the cleanliness of high-touch surfaces is of high importance. These high-touch surfaces (HTS) such as bedside tables, tray tables, bed frames, keyboards, bed rails, handles, and IV poles are common vectors for HAI transmission [1,4,10—12]. Therefore, the use of self-cleaning surfaces is desirable as it mitigates the risk associated with lapses in hand hygiene. Current techniques to treat HTS can be classified as either discrete or continuous. Discrete techniques include wiping the surface with disinfectants or detergents, hydrogen peroxide, steam vapour, ozone, or using UV lights or HINS (high-intensity narrow-spectrum light) While these techniques focus of the cleaning of contaminated HTS an alternate approach involves the use of materials or coatings that continuously protect the surface either by resisting microbial adhesion or actively killing microbes on the surface. In recent years, there has been an increase in the usage of HTS manufactured from copper and copper alloys to reduce HAIs. Unfortunately, the cost associated with replacing all current HTS with copper is infeasible. Hence, the development of antimicrobial polymer composite coatings has drawn significant interest as it allows for the coating of current HTS. Examples of currently used antimicrobial polymeric composites include Copper Armour (a copper/poly(methyl methacrylate) composite), Microban (silver zinc/epoxy composites), etc. The mechanistic studies of antimicrobial polymer composites used in high-touch surface are very limited; the antimicrobial mechanisms of polymeric materials in general healthcare applications would be used for high-touch surface even though in literature they are mostly focused on biomedical devices and implants surfaces, which are briefly discussed below.

The general antimicrobial action of polymeric materials can first be classified as either passive or active. Materials are passively antimicrobial when microbial species are not able to settle on the surface due to its inherent physico-chemical characteristics, whereas materials are actively antimicrobial if the material actively inhibits or kills pathogens. The mechanisms that act on bacteria, viruses and fungi differ due to the differences in the outer surface or membrane. As biological membranes are hydrophobic and negatively charged, the surface of a passively antimicrobial material is usually hydrophilic, negatively charged, or has a low surface free energy, repelling the infectious agents [13]. Polyethylene glycol (PEG) has been well studied in this regard and has shown effectiveness against *S. aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*. More importantly, however, is the use of PEG in specific configurations—as polymer brushes [14]—that enable the material to not only be antimicrobial but also anti-fouling. This behaviour is attributed to PEG's high chain mobility, large exclusion volume, and the steric hindrance effect of the highly hydrated layer [15], which prevent protein adsorption and bacterial adhesion [14]. The zwitterionic polymers and charged polyampholytes, for example, phosphobetaine, sulfobetaine, or phospholipid polymers [16] are also used to provide passive antimicrobial activity.

Active antimicrobial activity can be further classified as either biostatic or biocidal. Biostatic action refers to a surface that inhibits microbial replication. The biostatic surfaces can be suitable for coating certain medical instruments. This contrasts with biocidal action, which actively kills microbes. Of the two, biocidal activity is more desirable as it also prevents the microbes from replicating after leaving the surface [17]. It should be noted that what is biostatic against one organism may be
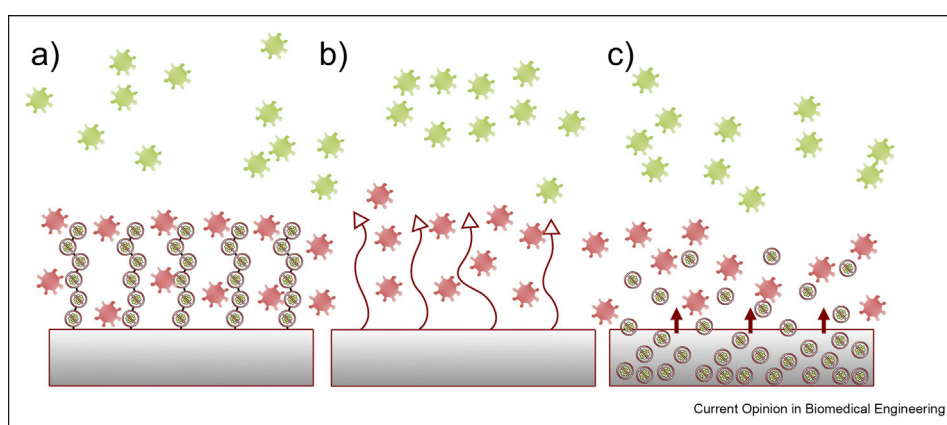
biocidal against another, and therefore, the definition of the activity is linked to specific organisms. Furthermore, the adage "the dose makes the poison" is somewhat applicable when discussing the spectrum of biostatic to biocidal activity.

Active antimicrobial activity can be enabled using polymeric biocides, biocidal polymers, or biocide-releasing polymers [8] (see Figure 1). Polymeric biocides are defined as the interconnection of repeating active biocidal units [13]. Biocidal polymers are macromolecules with at least one biocidal group embedded within their structure, which can damage the integrity of the infectious agent(s). The functional groups are usually antibiotics, positively charged biocides, or antimicrobial peptides [18]. It is determined by the antimicrobial repeating groups they contain. As for the contact killing, the polymeric surfaces are biocidal by themselves. While the mechanism of action is still unclear there are two well regarded hypotheses for different tethering length. For surface tethered small molecules the phospholipid sponge effect dominates, where the negatively charged phospholipids from the cell membranes are attracted by positively charged surface groups leading to damage to the phospholipid bilayer and cell death [19]. The polymeric spacer effect occurs when the tethering molecule is long enough for the biocide to penetrate the cell membrane. Once the phospholipid bilayer is broken, cellular content leaches out killing the microbial cells [20]. The same two mechanisms can also be utilized for antiviral activity against enveloped viruses as they are less stable than non-enveloped viruses, since the phospholipid bilayer has high susceptibility to physical disruption [21]. Biocide releasing polymers are materials loaded with biocides and hence their biocidal activity is not due to the polymeric matrix itself. Instead, the matrix acts as a carrier of the biocidal agents and releases them to contact and attack the targeted organisms [22].

With only one of the three mechanisms being discussed above—repelling, biocide-releasing and contact-active activities, antimicrobial polymers cannot always work sufficiently for practical applications as each of them has its respective inherent defects [23]. Therefore, multi-functional antimicrobial surfaces have been actively developed. Examples of combination repelling and contact-killing properties include the surface developed by Laloyaux et al., comprising surface attached magainin grafted with oligo(ethylene glycol) methacrylate. The contact-killing action of this surface is activated at room temperature with the polymer brushes stretched. It switches to repel microbes when the PEG brush structures collapse by increasing the temperature to over $35°C$ (T_{coll}) [24]. The combination of biocide-releasing and contact-active approaches has also been demonstrated to increase the antimicrobial efficiency and lifetime of antimicrobial activity of the entire system. Liang et al. combined N-halamine siloxane with quaternary ammonium salt siloxane to form a composite polyurethane coating. It was found that the coating displayed lasting antimicrobial activity due to the addition of the quaternary ammonium compounds. These contact-killing-QACs continued to provide antimicrobial action after the hypochlorite release system ceased to function, giving the coating long term functionality [25]. A similar behaviour could be achieved by the coating approach Li et al. developed based on a layer-by-layer assembled antibacterial coating with immobilized quaternary ammonium salts and releasable silver ions on a polystyrene surface. The antimicrobial efficiency of silver ion-releasing was accompanied by the contact-killing activity from the layer of quaternary ammonium compounds [26].

Figure 1

Schematic illustration of three typical types of antimicrobial polymers: **a)** polymeric biocides consisting of repeating biocidal units; **b)** biocidal polymers a macromolecule containing at least one biocidal group; **c)** biocide releasing polymers consisting of a matrix filled with a biocidal agent that releases over time.

Assessment method of antimicrobial polymers and composites

The evaluation of the antimicrobial activity of various composites and functionalized polymer surfaces is usually performed using live cultures of microorganisms exposed to the surfaces. The extent of survival can then be assessed using culture techniques, which is then compared to control surfaces having no antimicrobial activity. Although the antimicrobial assessment is often similar, the experimental details vary significantly among researchers and this lack of standardization results in difficulties in comparing the efficacy of various materials. To illustrate, Table 1 summarizes a few recent publications and the techniques reported.

Table 1

An overview of selected publications measuring antimicrobial efficacy on polymer-based surfaces.

Material	Microbes	Conditions	Measures	Ref.
Functionalized poly-lactic acid films	*E. coli* and *Bacillus subtilis*	Overnight cultures at 0.07 OD_{600}, 24 h droplet on polymer contact	Plate counts	[17]
Amphiphilic ternary polymers	*P. aeruginosa*, *E. coli*, *S. aureus*	Broth dilution method of polymer samples	Minimum inhibitory concentration	[31]
Functionalized polyurethane (PU)	*S. aureus*, *E. coli*, Vancomycin-resistant Enterococcus,	Broth incubation (5×10^7 CFU/mL) at 37°C for 16 h	Plate count	[32]
	E. coli	10^7 CFU of *E. coli* in 100 μL deposited on surface after 30 min samples were lightly rinsed	Live/dead staining with confocal microscopy	[32]
	SARS-CoV-2, enveloped TGEV, non-enveloped FCV	100 μL of virus suspension were added on the test sample, which were incubated for various times before the virus was recovered by vortexing the sample with medium.	50% tissue culture infective dose (TCID50) assay	[32]
Functionalized PU films	*S. aureus*, *S. epidermis*, *P. aeruginosa*, *E. coli*	10^6 cfu/mL submerged polymer incubation for 48 h at 37°C.	Plate counts	[33]
Functionalized silicone (Polydimethyl-siloxane also known as PDMS)	*S. aureus*, *E. coli*, *P. aeruginosa*	10^8 cfu/mL droplets on polymer for 3 h at 37°C with humidity.	Plate counts	[34]
Cuprous oxide (Cu_2O) particles bound with PU	SARS-CoV-2	5 μL of virus suspension were added on the test solid, which were incubated until the droplets were desiccated. The surface was soaked in 300 μL of medium.	50% tissue culture infective dose (TCID50) assay	[35]
Silver nanoparticle (AgNP)-coated polyurethane	HIV-1 and HSV-1/2	HIV-1: 200 μL of HIV suspension were incubated with the AgNPs-coated polyurethane. Viruses were collected and used to infect T cells.	Assayed by the observation of levels of viruses-induced syncytium formation and HIV-1-infected (GFP+) cells microscopy	[36]
AgNP-chitosan	Influenza A virus	Viral suspension was added to 250 μL AgNP-chitosan composite suspension. After 1 h, samples were centrifuged.	The supernatant was used to infect MDCK cells and the virus was titrated by TCID50.	[37]
Polyethylene coated with linear N,N-dodecyl,methyl-PEI	Non-enveloped poliovirus and rotavirus.	10 μL of a virus suspension was added on a coated slide and the droplet was sandwiched with a bare slide. After 30 min incubation at room temperature, the sandwiched slides were washed with cell culture medium.	Plaque assay	[38]

No matter the biological entity that is being examined, the overall antimicrobial testing process typically involves contacting the material with a volume of liquid biological suspension. This liquid volume is either kept as a liquid or dried onto the surface. The biological entities are either recovered from the surface by reapplying a liquid volume to remove them, or the assessment of biological load is done directly from the liquid being applied to the surface. For bacteria or fungi, plate counts are frequently used to determine their survival; however, it is also possible, especially if biocides are released from the polymer, to use zones of inhibition methods. Since these methods cannot account for microbes that are injured or simply inhibited, microscopic methods with live/dead stains are sometimes used for direct observations on surfaces. For viruses, various methods can be used to test their presence and viability; however, the viability is the most important and requires cell-based assays. These can include plaque assays, 50% tissue culture infective dose (TCID$_{50}$) and end-point dilution assays. The core of all these types of assays involves serial dilutions of a solution in which virus is thought to be present that is added to a permissive (and ideally optimal) host cell line. Results are determined by observing microscopic cytopathic effects caused by the virus. An alternative methodology can make use of virus vectors, genetically engineered to carry a gene that leads to the production of a reporter protein such as green fluorescent protein (GFP) [3,4]. The latter makes use of detecting the reporter protein instead of a cytopathic effect. Factors such as temperature, presence of ions, humidity, light, and pH can have a significant impact on the activity of a surface and controlling for a single set of values, while useful for comparisons can limit the applicability of the results. For example, the conditions under which an antimicrobial coating on a hospital bed side table is subjected are significantly different than the same coating on a water fountain. For this reason, while standardized tests are important to determine the relative efficacy of a surface, they should not be considered a golden standard as additional testing should be done.

Some standard methods for hard antimicrobial surfaces have been issued, although there are significant differences. A U.S. EPA interim method [27] uses specific strains of *P. aeruginosa* and *S. aureus* at 22°C and 30%–40% relative humidity for 1–2 h of contact time. However, it also specifies aggressive abrasion testing as it was initially developed for copper-coated surfaces and may not be realistically appropriate for polymeric composites. ISO 21702 [28] suggests the use of Influenza A and Feline calicivirus strains applied to antimicrobial polymer surfaces at 25°C with minimum 90% relative humidity for 24 h. ISO 22196 [29] likewise tests plastic surfaces using bacterial species *S. aureus* and *E. coli* applied for 24 h at 35°C and minimum 90% relative humidity. An OECD guidance document [30] expands upon and suggests methods similar to ISO 22196. While these standard methods are useful for comparing materials, there are concerns that the test conditions do not adequately replicate realistic scenarios for antimicrobial material usage in many environments, for example, lower humidity and temperature, or repeated and frequent contamination events via touch or aerosol deposition.
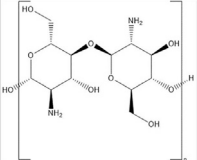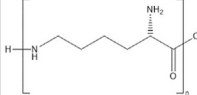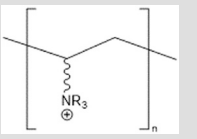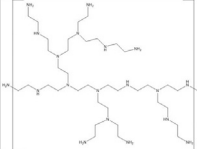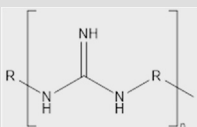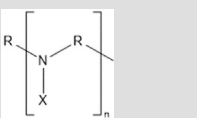
The research and published standard protocols that exist for testing antimicrobial surfaces are therefore seen to be quite varied. The continued development of standardized test methods is important to permit comparisons between materials, but caution should be taken to ensure the material functions correctly in its intended application and environment. This will include an understanding of the anticipated environmental conditions such as temperature, humidity, potential abrasion, chemical cleaning, and disinfection frequency, among others. The performance requirements for antimicrobial efficacy may also be quite important to characterize in terms of the kinetics of biocidal action. For example, an antimicrobial material being contaminated by touch several times per hour would require fast kinetics versus one contaminated infrequently, for adequate infection transmission prevention.

Strategies for developing antimicrobial polymer composites

The common strategies of developing antimicrobial polymer system can be divided into (1) adding intrinsic antimicrobial polymers, which contain inherent antimicrobial activity into polymer matrix; (2) adding antimicrobial organic compounds into polymer matrix, (3) adding antimicrobial inorganic fillers (micro/nano particles) into polymer matrix.

Intrinsic antimicrobial polymers

Generally, intrinsic antimicrobial polymers only perform as a stable antimicrobial coating when incorporated into another polymer matrix as they are water soluble leading to the dissolution of the coating on first contact with water. Several intrinsic antimicrobial polymers, their structure and mechanism of action are listed in Table 2. Of these polymers, chitosan is one of the earliest discovered antimicrobial polymers and widely studied. It is a polycationic polysaccharide and its natural antimicrobial activity against a broad spectrum of microorganisms is determined by the number of amino groups in the chitosan. Its antimicrobial mechanism varies based on the pH of the surroundings. When the pH is lower than pKa, amines in the chitosan can be protonated so that electrostatic interaction occurs between the positively charged polymer and the negatively-charged bacterial cell wall, whereas chelation and hydrophobic interaction predominate the antimicrobial performance of chitosan when pH is higher than pKa. While chitosan is typically used as an additive for coating textiles to

Table 2

List of intrinsic antimicrobial polymers, their structure and mechanism of action.

Intrinsic antimicrobial polymers	Monomer structure	Mechanisms of antimicrobial action	Remarks
Chitosan		Cell wall destruction by protonated amine groups when pH < pKa, chelation and hydrophobic interactions pH < pKa,	Water-soluble, biocompatible and biodegradable.
ε-poly-L-lysine		Cell wall destruction by a protonated amine groups	Biodegradable, nontoxic, thermostable and water-soluble.
QACs		Cell wall destruction by a cationic quaternary amine groups	High chemical stability.
Polyethyleneimine		Cell wall destruction by a protonated amine groups	Non-volatile, having long-term effectiveness and lower hemolytic activity.
Polyguanidines		Interrupting Ca^{2+} salt bridges present in the cell membrane leading to phase separation and disruption of the cellular membrane.	Water-soluble, nontoxic.
N-halamines		Through the oxidative halogen present in the structure that attacks the amino or thio groups of cell receptors.	Having long-term stability under both dry and aqueous condition.

provide antimicrobial activity [39], it has also been shown to provide antimicrobial activity when incorporated into polymer composites such as poly(methyl methacrylate) [40]. ε-poly-L-lysine (EPL) is an intrinsic cationic lysine homopolymer (n = 25–30) with ε-amino and α-carboxyl groups bonded by amides. EPL is generally used in food preservatives since it is a nontoxic, thermostable and water-soluble antimicrobial polymer. Its antimicrobial activity starts with electrostatic adsorption of cationic EPL onto the negatively-charged bacterial cell surface, leading to the disruption of bacterial outer membrane and leakage of essential compounds in bacterial cytoplasm. Both actions result in the death of bacteria [41]. Recently EPL has been shown to provide antimicrobial activity when incorporated in a poly(hydroxybutyrate) non-woven film. While effective, the composite was only useful as a single use item as the majority of the EPL was released within 1 h

[42]. PEI derives its antimicrobial activity from the primary, secondary and tertiary amine groups within its chain. With protonation of the respective amines, the primary, secondary and tertiary ammonium groups can become cationic. These cationic ammonium groups are commonly used to make antimicrobial polycations. In addition to PEI's inherent antibacterial property, the N-alkylated derivatives of PEI are the most studied synthetic polymers with antiviral activity, which can be non-covalently or covalently bound to different materials, including polymer composites [43]. Studies have proven that it has antiviral activity against different enveloped viruses, including Influenza [44], HIV [38,44], herpes simplex viruses [45], as well as non-enveloped poliovirus and rotavirus [46]. A practical application of derivatives of PEI against viruses was proposed by Larson et al. using N-dodecyl,methyl-polyethylenimine as a coating on latex condoms to decrease the infectivity of two

strains of herpes virus: HSV-1 and HSV-*2* [45]. Surfaces coated with quaternary ammonium salts (QACs) are frequently less active against non-enveloped viruses. Fulmer et al. developed antimicrobial latex coatings containing QACs and antimicrobial peptides, which were active against enveloped viruses, but were ineffective against feline calicivirus, a non-enveloped virus [47]. Tuladhar et al. demonstrate the lack of significant virucidal activity of immobilized QACs coated onto glass and plastic surfaces against poliovirus after up to 6 h of exposure [48]. On the other hand, Larson et al. showed that polyethylene slides painted with N,N-dodecyl,methyl-PEI efficiently reduced titers of the poliovirus and rotavirus [49].

Adding antimicrobial agents into a polymer matrix

While many materials are not intrinsically antimicrobial, antimicrobial activity can be achieved through the addition of biocidal agents into the matrix. The antimicrobial activities of polymers are based on their active biocidal agents. Positively-charged quaternary ammonium has been one of the most known antimicrobial agents to be chemically incorporated into polymeric matrix to produce synthetic antimicrobial polymers. Other studied agents include quaternary phosphonium and tertiary sulfonium as pendent antimicrobial agents. Regarding polycations, quaternary phosphonium and tertiary sulfonium obtain similar antimicrobial principle as quaternary ammonium. In addition to polycations, organic acids such as phenol and benzoic acid are also important antimicrobial additives. Phenols display the antimicrobial activity by disrupting the bacterial cell membrane, causing leakage of intracellular essentials as well as causing coagulation of cytoplasm. These lead to inhibition of bacterial growth. Though the antimicrobial mechanism of benzoic acid has not been clearly demonstrated in current studies, benzoic acid as a lipophilic acid has been found to interfere with the ability of *E. coli* and *Bacillus subtilis'* to uptake various amino acids and oxyacids.

Adding antimicrobial inorganic additives and micro/nano particles into polymer matrix

While significant research has focused on organic antimicrobial polymeric composites, inorganic particles have also been incorporated for antimicrobial purposes. Silver and copper are the most commonly used metallic antimicrobial agents taken the form of silver or copper micro/nanoparticles though recent research has also used various oxide particles such as zinc oxide, or magnesium oxide [50]. Generally, these particles release their respective metal ions that penetrate the cell and disrupt functions. The studies of the antibacterial mechanism of silver ions have shown that the ions interact with multiple membrane proteins, resulting in the disruption of the membrane and eventually cell death. Additionally, it was also found that silver ions are capable of disrupting the DNA replication cycle and interrupting the respiratory chain of bacteria. The virucidal activity of copper relies on the release of copper ions, that leads to reactive oxygen species generation, virus morphology alterations due to the loss of membrane structural integrity, and viral genome degradation [51]. Sagripanti et al. demonstrated that cupric ions were able to inactivate viruses with different biochemical and structural compositions, including enveloped or nonenveloped, single- or double-stranded DNA or RNA viruses [52].

The efficacy of these composites is highly dependant on the release rate of metal ions. There are three general approaches to increase release rate: the use of smaller filler particles to increase surface area, the use of a more hydrophilic matrix to increase diffusion of ions, and the use of metal oxide particles rather than metal particles as the oxide film is responsible for ion release. The first two approaches were demonstrated by Palza et al. [53] when comparing ion release rates of copper micro and nano particles in various polymer matrixes. While Delgado et al. demonstrated the last approach comparing copper oxide and copper nanoparticles in polypropylene [54]. Note that metal nanoparticles (NPs) have been found to effectively provide antimicrobial activity in polymer composite systems with greater performance than their microparticle analog. The smaller particles provide significantly higher surface areas and reactivity, also tend to provide extra functionalities to the NPs-polymer composite system as well as increase its mechanical properties. Lyutakov et al. has developed light-activated antimicrobial coatings against both *S. aureus* and *P. aeruginosa* by doping porphyrin and silver nanoparticles in polymethylmethacrylate. Under illumination, porphyrin absorbs light and produces reactive oxygen, affecting the release of silver ions [55].

Several studies have demonstrated the antiviral activity of AgNPs against different viruses, including hepatitis B virus [56], influenza virus [57], and SARS-CoV-2 [58]. AgNPs have high antiviral activity against enveloped viruses, but not against non-enveloped viruses. In contrast, Cu and cuprous compounds such as Cu_2O, CuI, and CuCl exhibit antiviral activity against both enveloped and non-enveloped viruses, and therefore, Cu-coated surfaces have received more attention [59]. However, studies evaluating antiviral effects of copper coated onto polymer composites are scarce, and to-date no study was available evaluating the antiviral efficacy of those surfaces against non-enveloped viruses. The general antiviral mechanism is believed to be associated with silver nanoparticles that directly interact with the virus surface proteins and the silver nanoparticles to block the entry of the viruses into cells [60]. However, due to AgNPs size and properties, several disadvantages have been reported such as inherent particle aggregation, that could reduce their antiviral capabilities over

time, and cytotoxicity and DNA damage when inhaled or ingested by humans in high quantities [51]. Therefore, AgNPs have been combined with different classes of materials as a strategy to fabricate materials with antiviral properties. Mori et al. synthesized AgNP/chitosan composites with antiviral activity against H1N1 influenza A. The antiviral effects of surfaces containing copper nanoparticles or polymer composites based on copper nanoparticles (CuNPs) are much less studied than AgNPs. Sundberg et al. demonstrated that the antiviral activity of CuNPs surfaces against influenza A is higher than that with conventional copper [61]. Most recently, CuNPs attracted attention because of their potential employment in face masks. Ahmed et al. described a new respirator mask against SARS-CoV-2 composed of a nanofibrous matrix of polylactic acid and cellulose acetate containing copper oxide nanoparticles and graphene oxide nanosheets [62].

Surface patterning for antimicrobial activity

While chemical design provides significant promise for finding novel polymers with antimicrobial activity, physical patterning can be used to imbue an inert material with antimicrobial activity or in addition to chemical design to improve antimicrobial activity. Strategies utilizing surface patterning to achieve antimicrobial activity are typically based off natural biostructures such as cicada wings that show bactericidal activity towards Gram-negative bacteria. Effective patterns used for these surfaces include nanospikes, nanoripples, and nanotubes [63]. While there are multiple articles focusing on metal and glass, fewer have investigated surface patterning on polymeric surfaces for this purpose. Generally polymeric surfaces can be patterned through soft lithography, stamping or laser ablation. Additionally, there are multiple factors to take into account when designing a surface pattern for antimicrobial activity. If bacteriostatic surfaces are desired nanotubes or nanoripples with sub 1 μm surface features are desirable as they reduce the adhesion of bacteria on the surface other approaches utilize self-healing, slippery liquid-infused porous surface (SLIPS), commonly made of microtextured poly(dimethyl siloxane) with a hydrophobic oil impregnating microwells in the surface [64]. If bactericidal surfaces are needed high aspect ratio structures such as nanospikes, nanowires or nanopillars are required with feature sizes under 100 nm. It is important that the structures are below 1 μm and have a high aspect ratio in order to provide a hostile environment to bacteria rather than shield them in the valleys of the structures. However, for repelling surfaces the aspect ratio has an inverse effect of adhesion as taller structures promote adhesion. While the exact mechanism for these surfaces is not yet known, they show promise as they can be generated on a polymeric surfaces and compliment other methods of antimicrobial activity [63]. Surface patterning of polymer was recently found by Sanjay et al. to improve the antimicrobial activity of composite surfaces by facilitating the exposure of copper particles to the surface, showing an interesting synergic effect of the addition of surface structure and biocidal fillers [65]. Another example of a combined approach utilizes lotus leaf inspired composites consisting of PDMS with a surface layer of silica nanoparticles functionalized with 3-(trimethoxysilyl)-propyldimethyloctadecyl ammonium chloride reported by Rauner et al. [66]. This combined approach of contact killing and surface patterning was demonstrated to be an effective method of retaining hydrophobicity after the addition of QAC groups.

Concluding remarks and perspectives

In summary, antimicrobial polymer composites for high-touch surfaces have seen significant developments over the past decade. These polymers can provide protection of people from the spread of infectious disease via objects in the environment. In many instances, the mechanisms of antimicrobial action are still not well understood. There have been several approaches for achieving antimicrobial activities, including the addition of intrinsic antimicrobial polymers, antimicrobial agents, or inorganic nano/microparticles to a polymer matrix, surface patterning with antimicrobial structures or a synergistic approach incorporating multiple of the above approaches in a single composite.

Major advances in the field have focused on the incorporation of antimicrobial agents within inert polymers to achieve antimicrobial activity with low toxicity, allowing safe handling and use in health care and similar environments. There is an emerging development of synthetic antimicrobial peptides (SAMP) that applies high throughput techniques to screen libraries of compounds to determine antimicrobial activity. By selecting acrylate monomers with various pendant groups to mimic antimicrobial peptides, an analog can be produced that is not susceptible to enzymatic degradation [67]. These emerging molecules might be used as novel additives in various HTS coatings as their stability and compatibility with polymer matrices will likely be improved. One underdeveloped area is the characterization methods for these surfaces. While individual research groups have developed reliable tests for determining the antimicrobial activity of a composite, these methods are not standardized, leading to difficulty comparing multiple sources within the literature. It is strongly recommended that standard testing protocols should be established in addition to the typical situational testing performed to confirm the material's applicability for a desired application and environment. Furthermore, while antibacterial or antiviral characterization is commonplace within the field, rarely is a material comprehensively tested for their antiviral, antibacterial, and antifungal properties. These

flaws have been pushed into the spotlight due to the current health crisis, where antimicrobial composites are essential for high touch surfaces such as hospital furniture and equipment.

During the pandemic, the usage of disinfectants and sterilization agents has increased exponentially leading to an increase of sterilizing agents in wastewater. Due to the liquid or water-soluble nature of many of these products, care must be taken to reduce the environmental impact of cleaning residues in our wastewater and ecological systems [68]. Additionally, chemical cleaning and disinfection of surfaces is known to be very dependent on the frequency and skill of the cleaners. For this reason, long lasting antimicrobial composites are of significant interest as the transfer of these problem chemicals into the environment are reduced due to their stability and ability to be recycled by other means. Furthermore, antimicrobial composites can be used in tandem with manual cleaning to add another layer of safety when manual disinfection fails to provide the necessary level of protection on its own. In addition to safer materials, the development of multi approach materials seeks to overcome the disadvantages associated with each strategy by incorporating multiple mechanisms of action into a single material. These approaches include surface patterning along with the incorporation of a biocide or antimicrobial nanoparticle to achieve both passive and active antimicrobial activity. Challenges exist that require addressing as the field grows, specifically the development of long-lasting, nontoxic or environmentally friendly antimicrobial polymers against a broad-spectrum of microbes with suitable properties under the environmental conditions of usage.

Declaration of competing interest

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

Acknowledgments

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Cobrado L, Silva-Dias A, Azevedo MM, Rodrigues AG: **High-touch surfaces: microbial neighbours at hand**. *Eur J Clin Microbiol Infect Dis* 2017, **36**:2053–2062. https://doi.org/10.1007/s10096-017-3042-4.

2. HAI Data | CDC. https://www.cdc.gov/hai/data/index.html. (Accessed 12 May 2021).

3. Walji S-D, Aucoin MG: **A critical evaluation of current protocols for self-sterilizing surfaces designed to reduce viral nosocomial infections**. *Am J Infect Control* 2020, **48**: 1255–1260. https://doi.org/10.1016/j.ajic.2020.02.008.

4. Walji S-D, Bruder MR, Aucoin MG: **Virus matrix interference on
** ** assessment of virucidal activity of high-touch surfaces designed to prevent hospital-acquired infections**. *Antimicrob Resist Infect Control* 2021, **10**:133. https://doi.org/10.1186/s13756-021-01001-x.
[An examination of soiling agents and protocols for bacteria and how they can be applied to examining the efficacy of anti-viral materials. This work also underscores how the preparation of virus can affect the evaluation of anti-viral activity and how it is important to establish controls that also investigate the effect of the recovery liquid on the host cells used to evaluate the viability of the virus.]

5. WHO multi-country survey reveals widespread public misunderstanding about antibiotic resistance, https://www.who.int/news/item/16-11-2015-who-multi-country-survey-reveals-widespread-public-misunderstanding-about-antibiotic-resistance. (Accessed 7 September 2021).

6. Namivandi-Zangeneh R, Wong EHH, Boyer C: **Synthetic anti-
* microbial polymers in combination therapy: tackling antibiotic resistance**. *ACS Infect Dis* 2021, **7**:215–253. https://doi.org/10.1021/acsinfecdis.0c00635.
[An in-depth review of combination therapies with various antimicrobial agents of synthetic antimicrobial polymers. Focuses on combating antibiotic resistant infections by utilizing combination therapies including nitric oxide, antibiotics, essential oils, and metal- and carbon-based inorganics as antimicrobial agents.]

7. Jamal M, Ahmad W, Andleeb S, Jalil F, Imran M, Nawaz MA, Hussain T, Ali M, Rafiq M, Kamil MA: **Bacterial biofilm and associated infections**. *J Chin Med Assoc* 2018, **81**:7–11. https://doi.org/10.1016/j.jcma.2017.07.012.

8. Siedenbiedel F, Tiller JC: **Antimicrobial polymers in solution and on surfaces: overview and functional principles**. *Polymers* 2012, **4**:46–71. https://doi.org/10.3390/polym4010046.

9. Bioseguridad Julieta: *Recent advances in antimicrobial polymers: a mini-review*. Bioseguridad; 2016.

10. Imani SM, Ladouceur L, Marshall T, Maclachlan R, Soleymani L, Didar TF: **Antimicrobial nanomaterials and coatings: current mechanisms and future perspectives to control the spread of viruses including SARS-CoV-2**. *ACS Nano* 2020, **14**: 12341–12369. https://doi.org/10.1021/acsnano.0c05937.

11. Birkett M, Dover L, Cherian Lukose C, Wasy Zia A, Tambuwala MM, Serrano-Aroca Á: **Recent advances in metal-based antimicrobial coatings for high-touch surfaces**. *Int J Mol Sci* 2022, **23**:1162. https://doi.org/10.3390/ijms23031162.

12. Chang T, Sepati M, Herting G, Leygraf C, Rajarao GK, Butina K, Richter-Dahlfors A, Blomberg E, Wallinder IO: **A novel methodology to study antimicrobial properties of high-touch surfaces used for indoor hygiene applications—a study on Cu metal**. *PLoS One* 2021, **16**:e0247081. https://doi.org/10.1371/journal.pone.0247081.

13. Francolini I, Donelli G, Crisante F, Taresco V, Piozzi A: **Antimicrobial polymers for anti-biofilm medical devices: state-of-art and perspectives**. *Adv Exp Med Biol* 2015, **831**:93–117. https://doi.org/10.1007/978-3-319-09782-4_7.

14. Yu K, Mei Y, Hadjesfandiari N, Kizhakkedathu JN: **Engineering biomaterials surfaces to modulate the host response**. *Colloids Surf B Biointerfaces* 2014, **124**:69–79. https://doi.org/10.1016/j.colsurfb.2014.08.009.

15. Zhang H, Chiao M: **Anti-fouling coatings of poly(dimethylsiloxane) devices for biological and biomedical applications**. *J Med Biol Eng* 2015, **35**:143–155. https://doi.org/10.1007/s40846-015-0029-4.

16. Liu L, Li W, Liu Q: **Recent development of antifouling polymers: structure, evaluation, and biomedical applications in**

nano/micro-structures. *Wiley Interdiscip Rev Nanomed Nano-biotechnol* 2014, **6**:599–614. https://doi.org/10.1002/wnan.1278.

17. Ojogbo E, Ward V, Mekonnen TH: **Functionalized starch microparticles for contact-active antimicrobial polymer surfaces**. *Carbohydr Polym* 2020, **229**:115422. https://doi.org/10.1016/j.carbpol.2019.115422.
    * *
    [Antimicrobial starch microparticles were synthesized utilizing Polyhexamethylene guanidine hydrochloride (PHGH). The starch microparticles were incorporated into a polylactic acid matrix with 10%wt starch showing a plateau in effectiveness. The PLA composites showed contact killing properties with no leaching of PHGH after a film was immersed in water for 72 h. The antimicrobial starch shows promise for incorporation into PLA based food packaging along with the possibility for utilization in other polymers]

18. Xue Y, Xiao H, Zhang Y: **Antimicrobial polymeric materials with quaternary ammonium and phosphonium salts**. *Int J Mol Sci* 2015, **16**:3626–3655. https://doi.org/10.3390/ijms16023626.

19. Bieser AM, Tiller JC: **Mechanistic considerations on contact-active antimicrobial surfaces with controlled functional group densities**. *Macromol Biosci* 2011, **11**:526–534. https://doi.org/10.1002/mabi.201000398.

20. Chrószcz M, Barszczewska-Rybarek I: **Nanoparticles of quaternary ammonium polyethylenimine derivatives for application in dental materials**. *Polymers* 2020, **12**. https://doi.org/10.3390/polym12112551.

21. Firquet S, Beaujard S, Lobert P-E, Sané F, Caloone D, Izard D, Hober D: **Survival of enveloped and non-enveloped viruses on inanimate surfaces**. *Microb Environ* 2015, **30**:140–144. https://doi.org/10.1264/jsme2.ME14145.

22. Macha IJ, Cazalbou S, Ben-Nissan B, Harvey KL, Milthorpe B: **Marine structure derived calcium phosphate-polymer biocomposites for local antibiotic delivery**. *Mar Drugs* 2015, **13**: 666–680. https://doi.org/10.3390/md13010666.

23. Wei T, Tang Z, Yu Q, Chen H: **Smart antibacterial surfaces with switchable bacteria-killing and bacteria-releasing capabilities**. *ACS Appl Mater Interfaces* 2017, **9**:37511–37523. https://doi.org/10.1021/acsami.7b13565.

24. Laloyaux X, Fautré E, Blin T, Purohit V, Leprince J, Jouenne T, Jonas AM, Glinel K: **Temperature-responsive polymer brushes switching from bactericidal to cell-repellent**. *Adv Mater* 2010, **22**:5024–5028. https://doi.org/10.1002/adma.201002538.

25. Liang J, Chen Y, Barnes K, Wu R, Worley SD, Huang T-S: **N-Halamine/Quat siloxane copolymers for use in biocidal coatings**. *Biomaterials* 2006, **27**:2495–2501. https://doi.org/10.1016/j.biomaterials.2005.11.020.

26. Li Z, Lee D, Sheng X, Cohen RE, Rubner MF: **Two-level antibacterial coating with both release-killing and contact-killing capabilities**. *Langmuir ACS J Surf Colloids* 2006, **22**:9820–9823. https://doi.org/10.1021/la0622166.

27. US EPA O: *Antimicrobial testing methods & procedures: interim method for evaluating the efficacy of antimicrobial surface coatings*. MD: EPA: Ft. Meade; 2020. Standard.

28. *ISO 21702:2019*; Standard 83.080.01 *Measurement of antiviral activity on plastics and other non-porous surfaces*. Geneva, Switzerland: ISO; 2019:20.

29. *ISO 22196:2011*; Standard 83.080.01 *Measurement of antibacterial activity on plastics and other non-porous surfaces*. Geneva, Switzerland: ISO; 2011:15.

30. **OECD guidance document on quantitative methods for evaluating the activity of microbicides used on hard non-porous surfaces - OECD**. In *Standard ENV/JM/MONO*. Organisation for Economic Co-operation and Development; 2013:121. 2013)11.

31. Pham P, Oliver S, Wong EHH, Boyer C: **Effect of hydrophilic groups on the bioactivity of antimicrobial polymers**. *Polym Chem* 2021, **12**:5689–5703. https://doi.org/10.1039/D1PY01075A.

32. Liu Q, Zhang Y, Liu W, Wang L-H, Choi YW, Fulton M, Fuchs S, Shariati K, Qiao M, Bernat V, Ma M: **A broad-spectrum antimicrobial and antiviral membrane inactivates SARS-CoV-2 in**

minutes. *Adv Funct Mater* 2021, **31**:2103477. https://doi.org/10.1002/adfm.202103477.

33. Wo Y, Xu L-C, Li Z, Matzger AJ, Meyerhoff ME, Siedlecki CA: **Antimicrobial nitric oxide releasing surfaces based on S-nitroso-N-acetylpenicillamine impregnated polymers combined with submicron-textured surface topography**. *Biomater Sci* 2017, **5**:1265–1278. https://doi.org/10.1039/c7bm00108h.

34. Li Z, Liu H, Xu X, Ma L, Shang S, Song Z: **Surface modification of silicone elastomer with rosin acid-based quaternary ammonium salt for antimicrobial and biocompatible properties**. *Mater Des* 2020, **189**:108493. https://doi.org/10.1016/j.matdes.2020.108493.

35. Behzadinasab S, Chin A, Hosseini M, Poon L, Ducker WA:
    * *
    A surface coating that rapidly inactivates SARS-CoV-2. *ACS Appl Mater Interfaces* 2020, **12**:34723–34727. https://doi.org/10.1021/acsami.0c11425.
    [A coating consisted of cuprous oxide particles bounded with polyurethane reduced SARS-CoV-2 titer by about 99.9% after 1 h of contact. This coating showed high durability and good adherence to glass and stainless steel. It can be used in several high touch surfaces that people may fear to touch during a pandemic, such as doorknob, a pen, and a credit card keypad button.]

36. Jana ID, Kumbhakar P, Banerjee S, Gowda CC, Kedia N, Kuila SK, Banerjee S, Das NC, Das AK, Manna I, Tiwary CS, Mondal A: *Development of a copper-graphene nanocomposite based transparent coating with antiviral activity against Influenza virus*. 2020:2020. https://doi.org/10.1101/2020.09.02.279737. 09.02.279737.

37. Borkow G, Gabbay J: **Putting copper into action: copper-impregnated products with potent biocidal activities**. *Faseb J* 2004, **18**:1728–1730. https://doi.org/10.1096/fj.04-2029fje.

38. Gerrard SE, Larson AM, Klibanov AM, Slater NKH, Hanson CV, Abrams BF, Morris MK: **Reducing infectivity of HIV upon exposure to surfaces coated with N,N-dodecyl, methyl-poly-ethylenimine**. *Biotechnol Bioeng* 2013, **110**:2058–2062. https://doi.org/10.1002/bit.24867.

39. Li J, Tian X, Hua T, Fu J, Koo M, Chan W, Poon T: **Chitosan natural polymer material for improving antibacterial properties of textiles**. *ACS Appl Bio Mater* 2021, **4**:4014–4038. https://doi.org/10.1021/acsabm.1c00078.

40. Yilmaz Atay H: **Antibacterial activity of chitosan-based systems**. *Funct Chitosan* 2020:457–489. https://doi.org/10.1007/978-981-15-0263-7_15.

41. Shima S, Matsuoka H, Iwamoto T, Sakai H: **Antimicrobial action OF ε-POLY-L-LYSINE**. *J Antibiot (Tokyo)* 1984, **37**:1449–1455. https://doi.org/10.7164/antibiotics.37.1449.

42. Dias YJ, Robles JR, Sinha-Ray S, Abiade J, Pourdeyhimi B, Niemczyk-Soczynska B, Kolbuk D, Sajkiewicz P, Yarin AL: **Solution-blown poly(hydroxybutyrate) and ε-Poly-l-Lysine submicro- and microfiber-based sustainable nonwovens with antimicrobial activity for single-use applications**. *ACS Biomater Sci Eng* 2021, **7**:3980–3992. https://doi.org/10.1021/acsbiomaterials.1c00594.

43. Mouritz AP, Galos J, Linklater DP, Ladani RB, Kandare E, Crawford RJ, Ivanova EP: **Towards Antiviral Polymer Composites to Combat COVID-19 Transmission**. *Nano Sel* 2021. https://doi.org/10.1002/nano.202100078. n/*a* (n/a).

44. Hsu BB, Yinn Wong S, Hammond PT, Chen J, Klibanov AM: **Mechanism of inactivation of Influenza viruses by immobilized hydrophobic polycations**. *Proc Natl Acad Sci USA* 2011, **108**:61–66. https://doi.org/10.1073/pnas.1017012108.

45. Larson AM, Oh HS, Knipe DM, Klibanov AM: **Decreasing herpes simplex viral infectivity in solution by surface-immobilized and suspended N,N-Dodecyl,Methyl-Polyethylenimine**. *Pharm Res* 2013, **30**:25–31. https://doi.org/10.1007/s11095-012-0825-2.

46. Larson AM, Hsu BB, Rautaray D, Haldar J, Chen J, Klibanov AM: **Hydrophobic polycationic coatings disinfect poliovirus and rotavirus solutions**. *Biotechnol Bioeng* 2011, **108**:720–723. https://doi.org/10.1002/bit.22967.

47. Fulmer PA, Wynne JH: **Development of broad-spectrum antimicrobial latex paint surfaces employing active amphiphilic**

compounds. *ACS Appl Mater Interfaces* 2011, **3**:2878−2884. https://doi.org/10.1021/am2005465.

48. Tuladhar E, de Koning MC, Fundeanu I, Beumer R, Duizer E: **Different virucidal activities of hyperbranched quaternary ammonium coatings on poliovirus and Influenza virus**. *Appl Environ Microbiol* 2012, **78**:2456−2458. https://doi.org/10.1128/AEM.07738-11.

49. Larson AM, Hsu BB, Rautaray D, Haldar J, Chen J, Klibanov AM: **Hydrophobic polycationic coatings disinfect poliovirus and rotavirus solutions**. *Biotechnol Bioeng* 2011, **108**:720−723. https://doi.org/10.1002/bit.22967.

50. Aničić N, Kurtjak M, Jeverica S, Suvorov D, Vukomanović M:
* **Antimicrobial polymeric composites with embedded nano-textured magnesium oxide**. *Polymers* 2021, **13**:2183. https://doi.org/10.3390/polym13132183.
[A composite consisting of poly-lactide-co-glycolide (PLGA), with nanotextured magnesium oxide microrods showed significant reductions in the viability of *S. epidermis*, *E. coli*, P. auregin, *S. aureus* and MRSA. This material shows promise as a coating for medical implants as the magnesium aids in integration of the implant while preventing colonization by foreign bacteria]

51. Rakowska PD, Tiddia M, Faruqui N, Bankier C, Pei Y, Pollard AJ, Zhang J, Gilmore IS: **Antiviral surfaces and coatings and their mechanisms of action**. *Commun Mater* 2021, **2**:1−19. https://doi.org/10.1038/s43246-021-00153-y.

52. Sagripanti JL, Routson LB, Lytle CD: **Virus inactivation by copper or iron ions alone and in the presence of peroxide**. *Appl Environ Microbiol* 1993, **59**:4374−4376.

53. Palza H, Quijada R, Delgado K: **Antimicrobial polymer composites with copper micro- and nanoparticles: effect of particle size and polymer matrix**. *J Bioact Compat Polym* 2015, **30**: 366−380. https://doi.org/10.1177/0883911515578870.

54. Delgado K, Quijada R, Palma R, Palza H: **Polypropylene with embedded copper metal or copper oxide nanoparticles as a novel plastic antimicrobial agent**. *Lett Appl Microbiol* 2011, **53**: 50−54. https://doi.org/10.1111/j.1472-765X.2011.03069.x.

55. Lyutakov O, Hejna O, Solovyev A, Kalachyova Y, Svorcik V: *Polymethylmethacrylate doped with porphyrin and silver nano-particles as light- activated antimicrobial material*. 2014. 20.

56. Lu L, Sun RW-Y, Chen R, Hui C-K, Ho C-M, Luk JM, Lau GKK, Che C-M: **Silver nanoparticles inhibit hepatitis B virus replication**. *Antivir Ther* 2008, **13**:253−262.

57. Xiang D, Chen Q, Pang L, Zheng C: **Inhibitory effects of silver nanoparticles on H1N1 Influenza A virus in vitro**. *J Virol Methods* 2011, **178**:137−142. https://doi.org/10.1016/j.jviromet.2011.09.003.

58. Almanza-Reyes H, Moreno S, Plascencia-López I, Alvarado-Vera M, Patrón-Romero L, Borrego B, Reyes-Escamilla A, Valencia-Manzo D, Brun A, Pestryakov A, Bogdanchikova N: **Evaluation of silver nanoparticles for the prevention of SARS-CoV-2 infection in health workers: in vitro and in vivo**. *PLoS One* 2021, **16**:e0256401. https://doi.org/10.1371/journal.pone.0256401.

59. Wang N, Ferhan AR, Yoon BK, Jackman JA, Cho N-J, Majima T: **Chemical design principles of next-generation antiviral surface coatings**. *Chem Soc Rev* 2021, **50**:9741−9765. https://doi.org/10.1039/D1CS00317H.

60. Haggag EG, Elshamy AM, Rabeh MA, Gabr NM, Salem M, Youssif KA, Samir A, Bin Muhsinah A, Alsayari A,

Abdelmohsen UR: **Antiviral potential of green synthesized silver nanoparticles of lampranthus coccineus and male-phora lutea**. *Int J Nanomed* 2019, **14**:6217−6229. https://doi.org/10.2147/IJN.S214171.

61. Sundberg K, Champagne Jr V: **Effectiveness of nanomaterial copper cold spray surfaces on inactivation of Influenza A virus**. *J Biotechnol Biomater* 2015. https://doi.org/10.4172/2155-952X.1000205. 05.

62. Ahmed MK, Afifi M, Uskoković V: **Protecting healthcare workers during COVID-19 pandemic with nanotechnology: a protocol for a new device from Egypt**. *J Infect Public Health* 2020, **13**: 1243−1246. https://doi.org/10.1016/j.jiph.2020.07.015.

63. Yang K, Shi J, Wang L, Chen Y, Liang C, Yang L, Wang L-N:
* **Bacterial anti-adhesion surface design: surface patterning, roughness and wettability: a review**. *J Mater Sci Technol* 2022, **99**:82−100. https://doi.org/10.1016/j.jmst.2021.05.028. ttps.
[A review focusing on the application of surface patterning to achieve antimicrobial activity. A significant portion of the review focuses on bacterial anti-adhesion surface patterning to reduce biofilm formation, though structure design for bactericidal capabilities are discussed as well]

64. Ye Q, Zhou F: **Antifouling surfaces based on polymer brushes**. In *Antifouling surfaces and materials: from land to marine environment*. Edited by Zhou F, Berlin, Heidelberg: Springer; 2015:55−81. https://doi.org/10.1007/978-3-662-45204-2_3.

65. Muralidharan SK, Bauman L, Anderson WA, Zhao B: **Recy-
* clable antimicrobial sulphonated poly (ether ether ketone) – copper films: flat vs micro-pillared surfaces**. *Mater Today Commun* 2020, **25**:101485. https://doi.org/10.1016/j.mtcomm.2020.101485.
[Composites consisting of sulfonated poly(ether ether ketone) and copper microparticles were cast in molds forming micropillars on the surface. While the size of the pillars was larger than the cutoff for biocidal activity, the vacuum casting process lead to an improved distribution of copper microparticles at the surface increasing antimicrobial activity compared to flat cast samples]

66. Rauner N, Mueller C, Ring S, Boehle S, Strassburg A, Schoeneweiss C, Wasner M, Tiller JC: **A coating that combines lotus-effect and contact-active antimicrobial properties on silicone**. *Adv Funct Mater* 2018, **28**:1801248. https://doi.org/10.1002/adfm.201801248.

67. Judzewitsch PR, Corrigan N, Trujillo F, Xu J, Moad G,
* Hawker CJ, Wong EHH, Boyer C: **High-throughput process for the discovery of antimicrobial polymers and their upscaled production via flow polymerization**. *Macromole-cules* 2020, **53**:631−639. https://doi.org/10.1021/acs.macromol.9b02207.
[A small library of synthetic antimicrobial peptides were produced using high throughput techniques showing a proof of concept for large scale screening with acrylate based amino acid analogs. Promising candidates were then scaled to multigram production using a slug flow reactor. Synthetic antimicrobial peptides found using these methods are promising candidates for incorporation into polymer matrices]

68. Dewey HM, Jones JM, Keating MR, Budhathoki-Uprety J: **Increased use of disinfectants during the COVID-19 pandemic and its potential impacts on health and safety**. *ACS Chem Health Saf* 2022, **29**:27−38. https://doi.org/10.1021/acs.chas.1c00026.