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Biomaterials: Antimicrobial surfaces in biomedical engineering and healthcare

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Abstract
Contamination of biomedical products with pathogenic microorganisms (bacteria, fungi, and viruses) is one of the main causes of hospital-acquired infections (HAI), and a major burden to the healthcare system. The development of biomaterials that can hamper the contamination of surfaces is vital to decrease patient-related infections in healthcare settings. In this landscape, this review identifies some of the latest antimicrobial strategies while paying particular attention to emerging antimicrobial biomaterials and nature-inspired antimicrobial surface topographies, which are rapidly finding application in the fabrication of biomedical engineering constructs.

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Antimicrobial surfaces, Biomaterials, Biomedical engineering.

Introduction

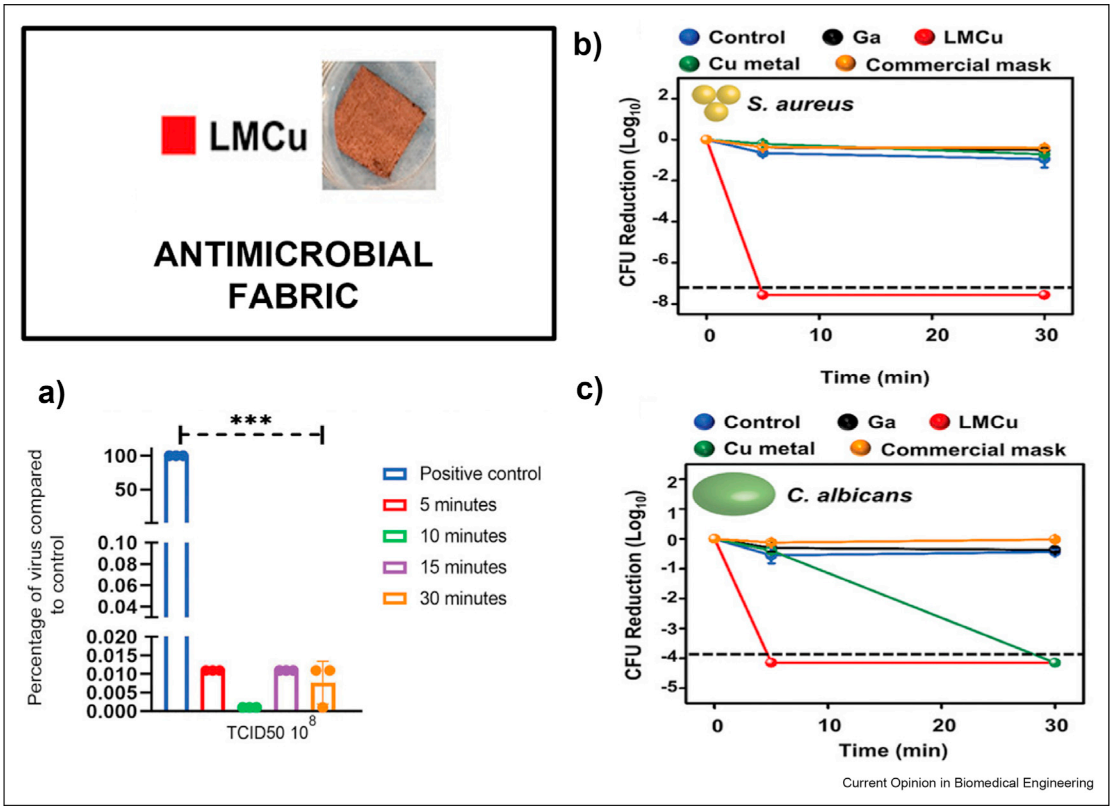
Prior to the SARS-CoV-2 pandemic, HAIs were estimated to account for approximately 100,000 deaths/year and 37,000 deaths/year in the US and Europe, respectively. Placing significant financial strain on the healthcare system, accounting for €7 billion in Europe alone [1]. Although the majority of HAIs are caused by bacteria (such as *Pseudomonas aeruginosa),* some fungi species (such as *Candida auris)* and viral strains (such as norovirus), as well as cross-infection have also been shown to contribute to HAIs [2,3].

The current global pandemic has raised public awareness on the importance of following best practices to prevent the spread of microorganisms from social distancing measures, hand hygiene, to face mask wearing. The introduction of these practices has helped reduce the spread of not only of SARS-CoV-2 but it has also reduced the cases of several notifiable infectious diseases, as reported by the ECDC [4]. In this scenario, the development of novel antimicrobial surfaces and biomaterial coatings that can halt microbial contamination and the spread of infection has gained increased attention [5]. In the context of fabrics as a potential source of contamination and infection within the hospital environment, novel antimicrobial fibre technologies have emerged [6]. As seen in Figure 1, a new fabric infused with gallium liquid metal copper alloy (LMCu) particles shows promising antimicrobial activity against bacteria (antibacterial), fungi (antifungal), and virus (antiviral) [7]. The development of such fabrics can be a game changer in the fight against SAR-CoV-2 with respect of personal protective equipment (PPE) for healthcare workers (i.e., coats, masks, and uniforms), and in bed/bath linens and gowns for patients [8].

Moreover, the contamination of biomedical implantable devices, catheters, prostheses, contact lenses, medical instruments, respiratory machines, and other hospital tools, are all potential sources for HAIs [9]. Over the decades, microorganisms have developed strategies to surpass many mechanisms of microbial disinfection and decontamination, through the emergence of multidrug resistant (MDR) microorganisms and the ability of some bacterial strains to produce biofilms [10,11]. This, in turn, makes HAIs increasingly difficult to be treated, often requiring prolonged intravenous systemic antibiotic therapy. If the infection is not resolved and it progresses to a severe infection, leading to septicaemia, surgery may be required to remove the infected device and necrotic tissue, and drain any abscesses [12]. Therefore, there is a strong need for novel strategies to be developed in order to suppress MDR microbial contamination, proliferation, and spread on surfaces such as those from medical implants.

The combination of biomedical engineering and materials science-based strategies is unveiling exciting new and vibrant discoveries in the field of antimicrobial research. Antimicrobial surfaces, in general, elicit either

Figure 1



Fabrics coated using gallium liquid metal copper alloy (LMCu) particles for antimicrobial fibre technology applications. a) Antiviral profile of LMCu-infused fabrics against influenza virus. b) Antibacterial profile of LMCu-infused fabrics against *S. aureus*. c) Antifungal profile of LMCu-infused fabrics against *C. albicans*. Reproduced with permission from Kwon et al. [7].

physical, chemical, or biological interactions with microorganisms (Figure 2).

In this review, antimicrobial surfaces are divided into three categories: (i) anti-adhesive—anti-biofouling surfaces, (ii) biocide attached—biocide release surfaces, which can be integrated with (iii) photocatalytic surfaces.

Emerging antimicrobial materials and strategies

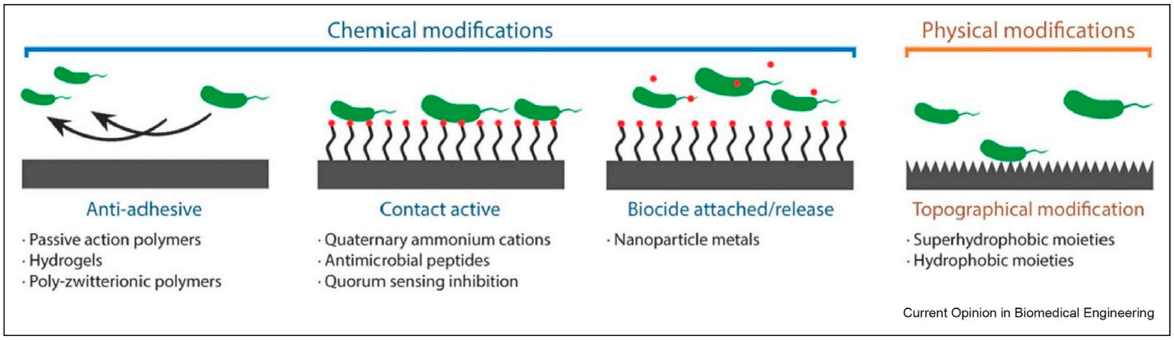
Anti-adhesive surfaces

Anti-adhesive/anti-fouling surfaces work by reducing the adhesion force between a solid surface and bacteria meaning that the bacteria can easily be removed before a biofilm is formed. Anti-adhesive strategies include superhydrophobic surfaces, zwitterionic polymers, and tailoring of surface nanostructure [14,15].

Physically-derived solutions capable of regulating bacterial colonisation by modifying current implant materials offer an enticing and appealing alternative to antimicrobial agents [16]. One such method that has yielded promising results is the anti-fouling effect of surface topography. Micro- and nanostructured surfaces that hinder bacterial adhesion but do not kill bacteria are ubiquitous in nature (Figure 3). Examples of anti-fouling surfaces found in nature include lotus leaves, shark skin, and rose petals. Many species of insects use their outer micro—nano structure to defend against bacterial colonisation, and this has inspired innovation around biomimetic antibacterial surface architectures for biomedical engineering applications [17—19].

A study conducted by Ishak et al. suggested that bacterial cell lysis is caused by the rupturing of the cell wall that was suspended between two neighbouring nanopillars [20]. However, several other articless have suggested models that differ from those proposed by Ishak et al. For example, Wu et al. suggested the impact of nanostructure density and height heterogeneity on the stretching degree of the bacterial cell envelopes [21]. Whilst these proposed models were significant in underlining the mechanism, they also came with certain shortcomings owing to the difficulty of bacteria—substrata interactions. Thus, it is evident that the specific interaction forces required to rupture the cell wall are currently unknown and require further investigation [22]. One technique based on similar methodologies

Figure 2



Surface modification strategies for antibacterial applications. Reprinted with permission from Uneputty et al. [13].

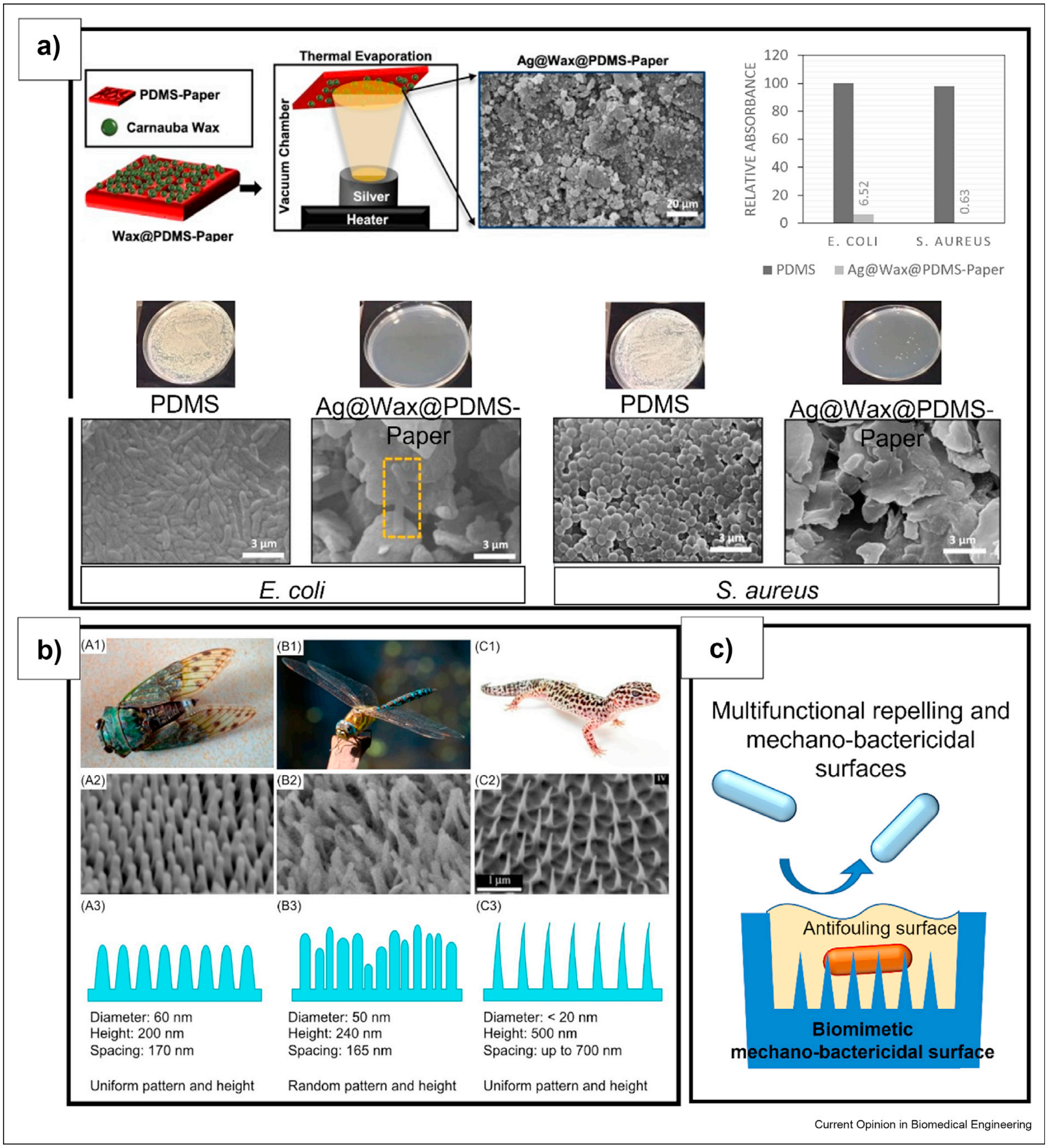
was recently carried-out by Hasan et al. who generated a novel nanoscale topography that inactivated bacteria as well as viruses. The team experimented with disks of aluminium 6063 and etched the material with sodium hydroxide for up to 3 hours which altered it into a ridged, hydrophilic surface. The nanostructured surfaces were subjected to nanoindentation tests and displayed excellent mechanical properties. This was a pivotal finding as it is the first record of a nanostructure that displayed both antibacterial and antiviral properties and so garners great potential in stopping the spread of infections arising from physical surfaces [23].

Another recent advancement in this field was achieved by the efforts of Wei et al. The study utilised vertical silicon nanowire arrays (SiN) and the biocidal tests conducted yielded interesting results as it displayed minimal evidence of bactericidal activity in relation to the surface itself. It was not until lysosome was incorporated that bacteria-killing capabilities were demonstrated, with SiN-PMAA/Lys surfaces showing the highest killing efficiency of more than 95%. These results highlight that whilst the surface did not confer bactericidal activity, it's topography and high surface area were paramount in retaining lysosomes, which in turn killed suspended and attached bacteria [24]. This study contrasted to others in its experimental framework as it outlined that research suggesting topographic cues are the causation of inhibiting bacterial adhesion can often be misconstruing. This is due to the fact that topographic cues are often reported with the chemical action of materials that constitute the coatings. This lack of distinction that can be made in such experiments has proved to be damaging to current knowledge in antimicrobial surfaces and so it is crucial that experimental frameworks take this into account in the future via the inclusion of samples that are absent of chemical action [25].

Producing bioinspired surfaces on a large scale in a cost-effective manner is technologically challenging and is an aspect that needs to be addressed [26]. Progress has recently been made in relation to this, as there are currently a number of techniques that are applicable for various materials. Ozkan et al. synthesised superhydrophobic antibacterial copper coated polymer films via aerosol assisted chemical vapor deposition (AACVD). AACVD was successful in combining polydimethylsiloxane (PDMS) and copper nanoparticles (CuNPs), which in turn fabricated a novel superhydrophobic antibacterial surface [27].

There are a number of bactericidal surfaces in nature such as cicada wings and dragonfly wings. The investigation into these natural bactericidal materials shows promise [17,28,29]. In an effort to understand the influence of surface topography on bacteria—surface interactions, Flynn et al. produced various mouldings from polypropylene glycol (PEG) to replicate the wings of cicada. Water swollen PEG allowed the controlled formation of larger pillars with enhanced bactericidal efficiency [30]. In addition, Fisher et al. carried-out research on diamond nanocone-patterned surfaces, representing biomimetic analogues of the naturally bactericidal cicada fly wing and observed its antibacterial activity. Two diamond nanocone surfaces were fabricated and SEM was then used to determine their morphology [16]. It was observed that surface B showed significantly higher bacterial activity than surface A. This research was important because it revealed that size variance, nonuniformity, and decreased density of nanocone arrays, such as surface B may benefit bacterial activity [16]. These findings were similar to that of Green et al. who documented the highly bactericidal nature of a gecko skin and contrasted it versus various materials. Numerous physical theories were put forward in an effort to elucidate the surface's bacterial rupturing mechanisms and these included compression, stretching, tearing and piercing [31]. Future research must focus on identifying the underlying mechanism behind the higher killing efficiency of these nature inspired surfaces and whilst they confer great promise; further

Figure 3



Antimicrobial surface strategies. a) Antifouling of superhydrophobic surfaces based on Ag@Wax@PDMS-Paper. Reprinted with permission from Sahin et al. [33]. b) Naturally occurring mechano-bactericidal surfaces: of Cicada, dragonfly and gecko, including SEM and schematic images of individual topographies. Reprinted with permission from Ishak et al. [20]. c) Combination of both antifouling and mechano-bactericidal strategies for the development of enhanced multifunctional surfaces.

work is required to understand these underlying principles and mechanisms [32].

Biostatic and biocidal surfaces

Contact-active antimicrobial surfaces work to kill microbes without the release of biocides. Generally, they either (i) optimise a spacer effect in which the biocide is attached to the surface through a polymer chain, allowing the biocide to reach and perforate the cytoplasmic membrane of the bacteria; or (ii) positively-charged quaternary ammonium compounds (QACs) can kill the bacteria by detaching phospholipids from their cell membranes [34].

Antimicrobial polymers are a promising area of research against microbial contamination due to their versatile chemistry, and the subsequent ability to tailor properties/performance [35]. Inherently antimicrobial polymers are of particular interest due to their intrinsic antimicrobial activity. Recently, hyaluronic acid-based composite films were found to be bacteriostatic [36–38]. Produced films were optimised in terms of their mechanical and antibacterial performance through the incorporation of carbon nanofibers. These materials were targeted as potential therapeutic coatings on dressings for wound healing [39]. With a further study showing that the antibacterial behaviour of a Schiff base generated from *O*-amine functionalised chitosan exhibited better antibacterial activity than chitosan and *O*-amine functionalised chitosan equivalents [40].

Antimicrobial peptides are naturally occurring antimicrobials with a broad spectrum of antimicrobial activities, that can be used as an alternative to antibiotics. The production of materials containing bioinspired antimicrobial peptides (AMPs) is proving to be a promising strategy in addressing infectious conditions and preventing bacterial attachment and biofilm formation on surfaces. These antimicrobial peptides (AMPs) can be engineered to have broad antimicrobial activity and are proving especially effective against bacteria immune to traditional antibiotics, while exhibiting excellent biocompatibility [41,42]. Many microbes and pathogens can be extremely hard to target and kill due to their complex membranes. Computer-aided design of AMPs can gather critical information on chemical parameters and bioactivities in AMP sequences, allowing for modes of prediction to assess a candidate sequence's antibacterial potential before chemical synthesis [43]. This also allows the potential for AMPs to be computationally designed for specific activity against specific viruses through the utilisation of a bioinformatics, protein engineering, and de novo design [44].

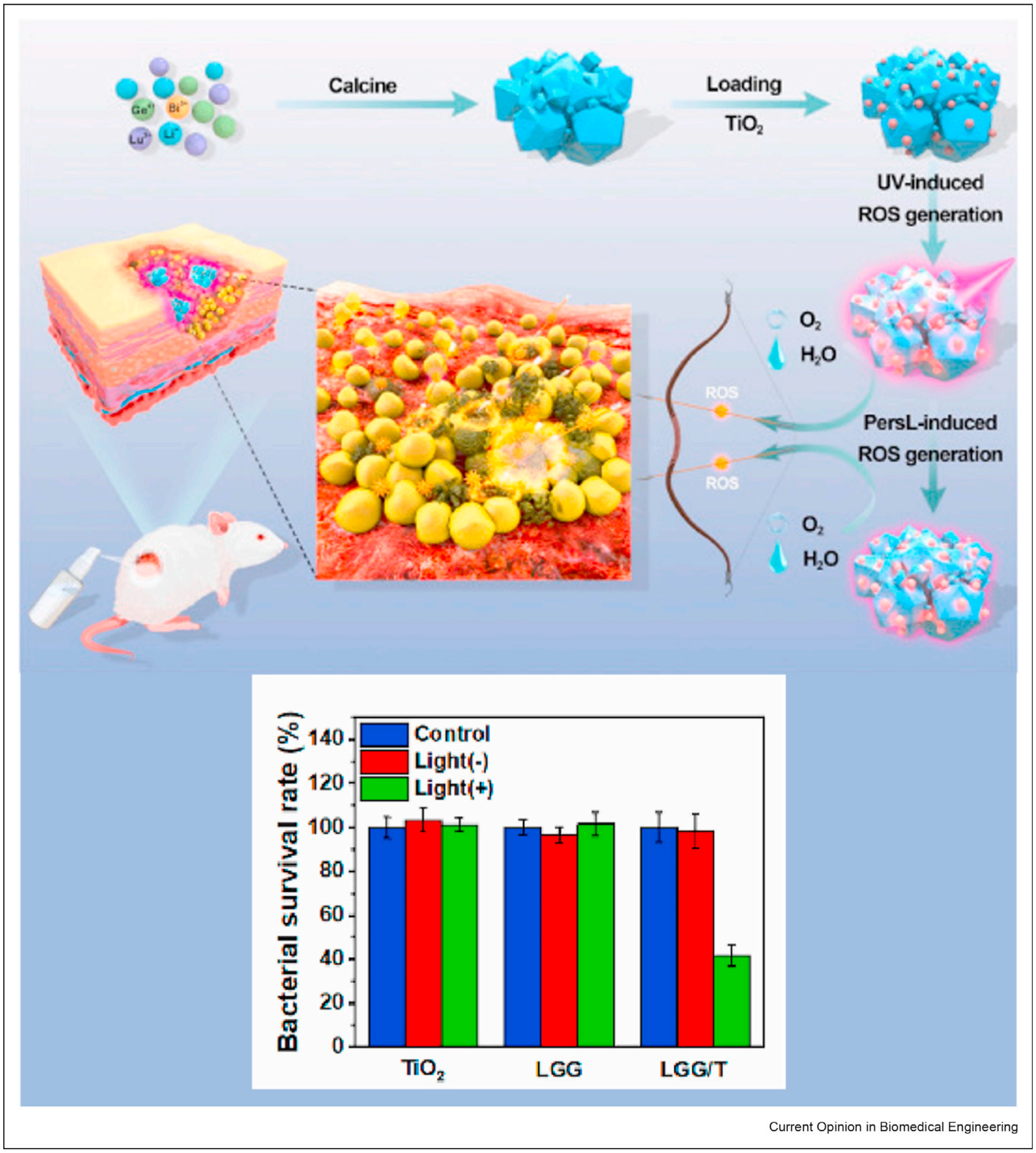
The use of hybrid polymeric/metal antimicrobial coatings have also undergone numerous studies in recent years. Hazer et al. reported a polymer-based Ag nanoparticle (NP) coated Titanium screws that displayed antimicrobial properties and inhibited biofilm formation. These modified screws were promising in that they conferred resistance to tapping forces as the Ag NPs were still attached to their surface after 21 days of implantation in rabbits [45]. Whilst studies such as these are promising due to the excellent antibacterial effects they display; they are also not without controversy owing to their metallic nature. Unfortunately, there is currently a lack of studies based on these hybrid polymeric-metal coatings that simultaneously observe the material's effects on both bacteria as well as eukaryotic cells [46]. While multifunctional sustainable lignin-based hydrogels that (1) are robust and elastic, (2) have strong antimicrobial activity, (3) are adhesive to skin tissue and various other surfaces, and (4) are able to self-mend are also showing enormous potential as future materials for healthcare applications [47].

A recent approach that has exhibited great promise in preventing bacterial infections involves the use of antibacterial biomaterials that are deposited on device surfaces to help mitigate bacteria attachment [48]. Bacteria have a proclivity for attaching to the surfaces of tissues or implants whilst producing extracellular polymeric substances (EPS) that form bacterial biofilms, which often result in pathogenic infections [49,50]. However, recently polymer coatings have shown a great ability in combating these microorganisms. The use of anti-adhesive coatings can be used alongside bactericidal surfaces to yield promising synergistic results. Yan et al. exploited a reversible, non-leaching bacteria-responsive antibacterial surface by manipulating the hierarchical polymer brush architecture. This involved the incorporation of a pH-responsive polymer outer layer into the bactericidal background layer, which functioned as an actuator to modulate the surface behaviour of the hierarchical surface, as per Figure 1 [51]. The findings show that this hierarchical surface could reversibly transform between bactericidal and bacteria–repellent properties via control of pH [52]. It is clear that future research into such multifunctional materials that carry out adaptive antibacterial activity without additional reloading of antimicrobial agents will be highly beneficial in the fight against infections as it will increase the longevity of the surface's antimicrobial functionality [53].

For example, Zhao et al. derived polymeric coatings that resulted in semi-interpenetrating polymer networks (SIPN) and conferred both antifogging and antimicrobial functions. It was discovered that the antifogging activity was attributed to the material's hydrophilic/hydrophobic equilibrium, while the antimicrobial effect was extracted from the hydrophobic quaternary ammonium compound. These coatings were also effective in killing both Gram-positive and Gram-negative bacteria [54]. Such multifunctional coatings are rare in current literature due to their novelty and further research is currently needed. Progress with these coatings will mark a significant advancement in antimicrobial surfaces as this multifunctionality provides an extra layer of protection to the patient [25].

Milo et al. described a pH-responsive hydrogel surface coating for urinary catheters with two layers that conferred notable antibacterial properties [55]. When the urinary pH was elevated due to infection, the poly (methyl methacrylate-co-methacrylic acid) layer swelled and released a dye, causing a visual colour transition. The dual functionality of this surface was remarkable in that it not only reduced bacterial populations but also provided an early warning of infection. Further investigation into similar materials could be highly beneficial as early detection of pathogens is instrumental to their mitigation [55]. However, as pH varies within the human body, other triggers have been investigated [56]. For example, Zhou et al. developed a hydrogel that reacts to pathogenic bacteria's toxins or enzymes. Gelatin methacryloyl (GelMA) hydrogels were applied to wound dressings and conferred the ability to selectively suppress pathogenic bacteria. The hydrogel also contained a vesicle that held a dye, which turned fluorescent when it was diluted due to degradation of the vesicle membrane, thereby highlighting infection. This mechanism yields great promise as it could detect infection and react to pathogenic bacteria whilst facilitating wound healing [54]. It is clear that these hydrogels hold the key in the fight against antibiotic resistance as they respond to biological stimuli and become active when the need is greatest [56].

Figure 4



Self-cleaning antibacterial photocatalytic biomaterial based on thermo-responsive hydrogel-loaded $LiLuGeO_4:Bi^{3+}/TiO_2$ (LGG/T) for wound treatment. Reprinted with permission from Liu et al [65].

Photocatalytic surfaces
Photocatalytic oxidation is being investigated as a possible alternative to antimicrobial coatings within a hospital environment. These surfaces usually contain photocatalytic metal oxides such as TiO_2 that generate OH radicals in the presence of UV-A light, oxygen, and water, and these OH-radicals destroy bacteria (shown in Figure 4). TiO_2 has been used extensively for photocatalytic applications recently as it shows high stability and photoactivity, low cost and it's nontoxic [57]. TiO_2 does however have limitations such as a large band gap and high recombination rates and so it is often modified using metal oxides [58].

For example, Pedroza-Herrera et al. synthesised coper-doped TiO_2 nanoparticles prepared by sol–gel deposition followed by microwave hydrothermal treatment that achieved a large band gap reduction with low levels of doping. These nanoparticles show remarkable antibacterial properties, without any cytotoxicity to blood cells. This method incorporates the photocatalytic oxidative attack with the leaching of copper ions to yield effective antibacterial results [59].

Non-metallic elements can also be used to modify TiO_2 such as SiO_2, nitrogen, and fluorine as they can improve photocatalytic activity with minimal toxicity. Janpetch et al. developed a hybrid nanocomposite with TiO_2 nanoparticles and bacterial cellulose doped with both fluorine and nitrogen. This material had an enhanced visible-light sensitivity and high photocatalytic disinfection activity under fluorescence light of both Gram-positive and Gram-negative bacteria [60].

A thermal spray technique is used to fabricate these photocatalytic coatings. This process is a one-step fabrication route and through chemical synthesis, element doping, it can be used as anti-fouling self-cleaning surfaces and for visible light induced sterilisation [61–64]. Despite successful results using the thermal spray method in fabricating photocatalytic coatings, published studies on this application and its related disinfection mechanisms are not well understood so there is opportunity for further research.

Final considerations
This review outlines the latest materials and methods that are currently being deployed to develop and enhance antimicrobial surfaces. An approach where coatings release antimicrobial agents upon attachment of specific bacteria to the surface is producing promising results. Polymers and biopolymers are at the forefront of this technology and incorporating multifunctionality into their mechanisms will help remedy modern medicine's issue of antibiotic resistance. Hybrid polymeric-metal coatings have seen significant advancements but are currently not without controversy due to the potential harm they can cause to eukaryotic cells. It is essential that future research on such materials include studies on both its cellular and antimicrobial behaviour. Stimuli-responsive hydrogels are another important class of biomaterial with growing recent interest. With enzyme responsive gels of particular interest due to their ability to attack bacteria directly whilst detecting infections early. Novel approaches for designing an antibacterial surface mediated by topographical features are also gaining traction. Significant progress has been made with manufacturing techniques used to synthesise these intricate surfaces. The use of photocatalytic surfaces synthesised by thermal spray is gaining interest. Combining one or more antimicrobial strategy can lead to a more robust approach to deal with dangerous pathogenic microorganisms, which can enable surfaces with multifunctionality to reduce adhesion, biofilm formation, and biostatic or biocide properties.

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.

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- •• of outstanding interest

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This study discusses the swelling characteristics of PEG to enhance the bacterial properties of surface topography. This was performed with a minimal loss of feature resolution and so greatly benefitted the performance of the surface. This study was crucial as it showed that there are many more aspects of bio inspired surfaces that are yet to be discovered.

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