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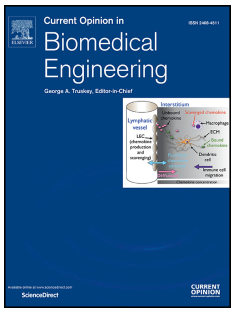

Science-based strategies of antibacterial coatings with bactericidal properties for biomedical and healthcare settings

Rakesh Pemmada, Aishwarya Shrivastava, Madhusmita Dash, Kuiyan Cui, Prasoon Kumar, Seeram Ramakrishna, Yubin Zhou, Vinoy Thomas, Himansu Sekhar Nanda

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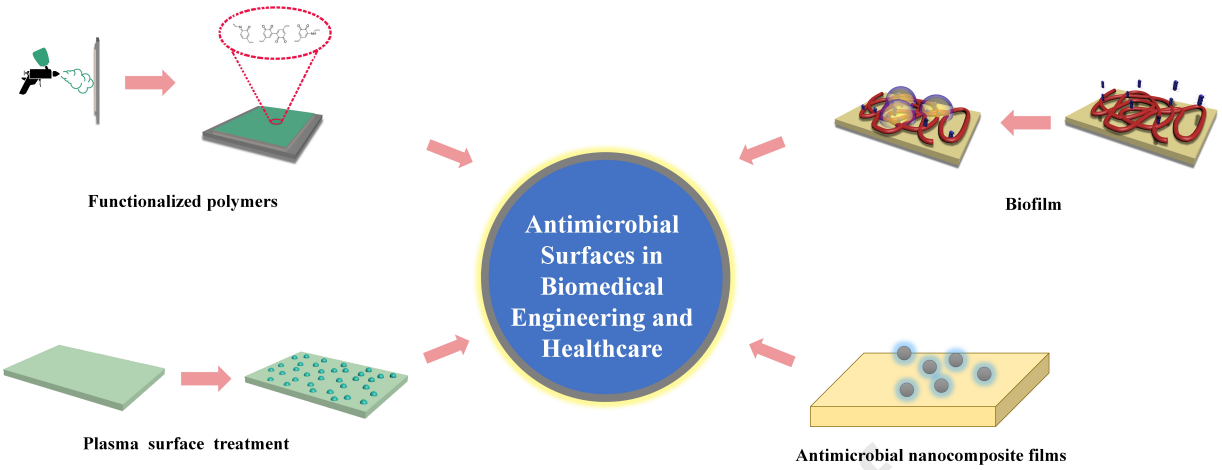


Science-based strategies of antibacterial coatings with bactericidal properties for biomedical and healthcare settings

Rakesh Pemmada[1,2], Aishwarya Shrivastava[1,3], Madhusmita Dash[4], Kuiyan Cui[5], Prasoon Kumar[6], Seeram Ramakrishna[7], Yubin Zhou[5, *], Vinoy Thomas[2, *], Himansu Sekhar Nanda[1, 3,8, *]

[1]Biomedical Engineering and Technology Lab, Discipline of Mechanical Engineering, PDPM Indian Institute of Information Technology Design and Manufacturing Jabalpur, , Madhya Pradesh 482005, India

[2]Department of Materials Science and Engineering, University of Alabama at Birmingham, Birmingham, AL 35294, USA

[3]International Centre for Sustainable and Net Zero Technologies, PDPM-Indian Institute of Information Technology Design and Manufacturing Jabalpur, Dumna Airport Road, Jabalpur 482005, Madhya Pradesh, India

[4]School of Minerals, Metallurgical and Materials Engineering, Indian Institute of Technology Bhubaneswar, Arugul, Odisha 752050, India

[5]Guangdong Provincial Key Laboratory of Research and Development of Natural Drugs, and School of Pharmacy, Guangdong Medical University, Dongguan 523808, PR China

[6]Biodesign and Medical device laboratory, Department of Biotechnology and Medical Engineering, National Institute of Technology Rourkela, Rourkela 769008, Odisha, India

[7]Centre for Nanotechnology & Sustainability, Department of Mechanical Engineering, Faculty of Engineering, National University of Singapore, Singapore 117576, Singapore

[8]Terasaki Institute for Biomedical Innovation, Los Angeles, California 90064, USA

Corresponding authors:

Prof. Yubin Zhou[5, *]: zybresearch@126.com (YZ), Tel: +86-0769-22896561

Prof. Vinoy Thomas[2, *]: vthomas@uab.edu (VT), Tel: +1 (205) 975-4098

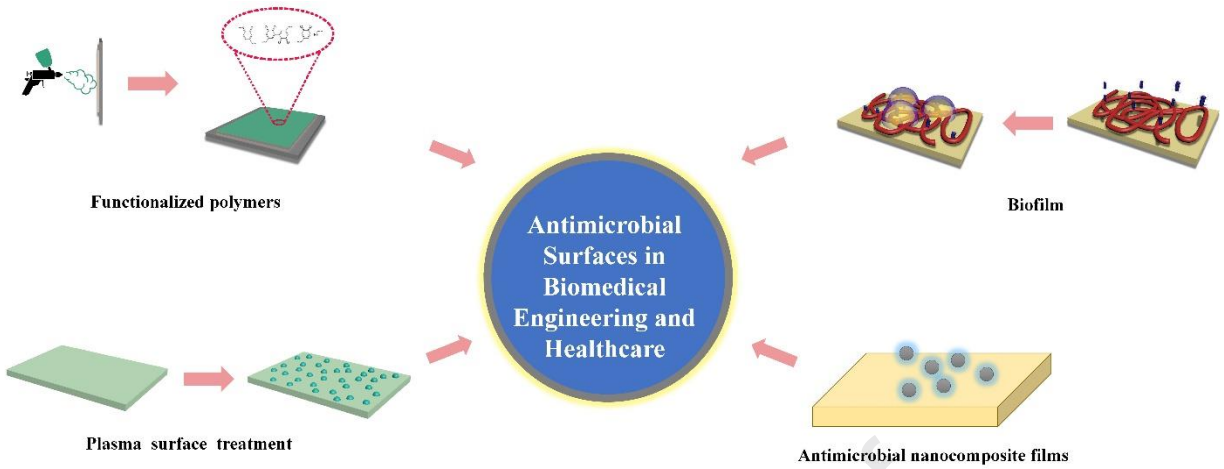
Prof. Himansu Sekhar Nanda[1, 3,8, *]: himansu@iiitdmj.ac.in (HSN), Tel: +91-761-2794429

Abstract

Contamination transmission in biomedical and healthcare settings is a significant challenge due to inadequate microbiological protection from anti-infection agents and disinfectants. Antimicrobial surfaces have been used as a current hygiene method to combat the growing microbes. Interestingly, several approaches have been developed to block biofilm formation by integrating the biocidal agents. Currently, the primary focus is on creating a contact-killing surface or a surface that may reduce the microbial load to a level below threshold. This review focuses on introduction of antimicrobials into the surfaces through various science-based strategies for reducing the bacterial contamination within different medical services environment. This incorporates effectively settled methods, and strategies consolidating inorganic and natural biocides with bactericidal properties into the polymer matrix and surface coatings to reduce the bacterial contamination.

Keywords: Biomedical; polymers; biocides; coatings; surface modification; bactericidal; antimicrobial

Graphical abstract



41

1. Introduction

42

43 The quality of life is gradually improving as a result of advanced surgical procedures and the
44 implantation of biomedical devices [1]**.** Currently, implants find their applications in various parts
45 of the body like orthopedic, cardiovascular, dental, and many others. To develop these implants,
46 diverse materials have been studied such as metals, metallic alloys, ceramics, polymers, polymer
47 composites, and others [2]**.** Healthcare systems assay to limit the contamination hazard on these
48 temporary implants by taking preventive measures at regular intervals [3]. These safeguard
49 substitution plans decree appreciable expenses to medical and healthcare systems. Enhanced
50 methodologies in sterilization have much diminished the recurrence of the initial phase
51 contaminations in implants. The prevalence of diseases that developed after several weeks or
52 months after surgery poses to be a major problem. Such crucial diseases might have occurred by
53 the planktonic microscopic organisms coursing in the vascular framework. Regardless of the
54 significant attempts in fabricating implantable biomedical devices, bacterial diseases persist due
55 to bacterial attachment and their growth on the surfaces [4]. In fact, bacterial adhesion on the
56 implants is regarded as one of the most significant global healthcare challenges, owing to its risk
57 of severe hazardous infections.

To reduce pathogenic bacteria-associated complications, bacterial adherence and colonization on the implants and devices should be considerably reduced. Many researchers focused on engineering the surface chemistry of the materials by making a hostile environment for bacterial adhesion and growth creating an antibacterial surface [5]. Generally, the antibacterial surfaces on the implants can be achieved by precise release of antibacterial agents, maintaining a bactericidal or antifouling surface using contact killing strategies [6]. Antibacterial coatings or antifouling polymers were also used as antibacterial strategies to mitigate the bacterial colonization. Several surface coatings have been developed for implants and devices using embedded antimicrobial nanoparticles, functionalized polymers, and inorganic-organic hybrid materials [7]. The bacterial species are usually targeted with the functional molecules through antifouling surfaces with antibacterial agents [8]. Due to the advantages of chemical modification, diverse materials are being employed with relatively lower fabrication costs. Although functional coatings demonstrate promising features, they usually undergo severe challenges like drug resistance, delamination, and hydrolytic degradation. Biomimetics has influenced materials science and engineering to aid the fabrication of advanced materials to mimic the native function of tissues or organs [9]. Some of the natural surfaces that show excellent antimicrobial properties prevent bacterial adhesion [10]. Apart from the natural surfaces, biomimicking can create the synthetic structures that mimic the surfaces with an antibacterial effect[11].

Hospital patients are at risk of communicable diseases in addition to the infectious disorders caused by microbes. Numerous individuals get sick while receiving the medical care as a result of microorganisms found in the hospital settings, on the medical staff, or on medical equipment. Nosocomial infection usually affects the patients and deteriorate their health and well being. The implementation of successful antimicrobial coatings can reduce the morbidity of nosocomial

infections caused due to the use of percutaneous, interventional, and implanted medical devices such as implantable cardioverter defibrillators, coronary stents, artificial hips, and contact lenses [12][13][14]

This review provides an expansive outline on bacterial contamination in the healthcare settings and the use of antibacterial strategies to mitigate those issues. Functionalized polymers, antimicrobial nanoparticle, and plasma surface modification as some of the science-based strategies are innately concentrated. It also provides an overview of most recent developments on antibacterial coatings, including the mechanism(s) by which the key component of the coating inhibits the growth of the biofilm formation. The article ends with a viewpoint on strategies implemented for biomedical and healthcare settings to protect from bacterial infections creating an antibacterial coating with bactericidal properties.

2. Development of biofilm

A biofilm is a cluster of microbial communities of the cells that are attached to a surface and embedded in a self-secreted matrix. This extracellular matrix consists mainly of the insoluble polysaccharides like alginate, proteins, lipids, flagella, pili, and eDNA [15]. Bacterial adhesion to a surface is dependent upon the surface topography and roughness. The variables affecting this adhesion and biofilm formation are electrostatic interactions, van der waals forces, hydrophobicity, and steric hindrance [16]. After adhering to a surface irreversibly, the microscopic organisms start to increase their number, co-exist, and produce an insoluble network of exopolymers to form the microcolonies. The development of a full-grown biofilm takes place, when the microcolonies are infiltrated by another microbial species. Such mature biofilms present a threat to the host because the microorganisms enclosed inside have the potential to detach and transmit the infections [17].

The development of a mature biofilm is a complex process, which includes an initial irreversible attachment, maturation I and II and finally, dispersion as shown in the **Figure 1** [18].

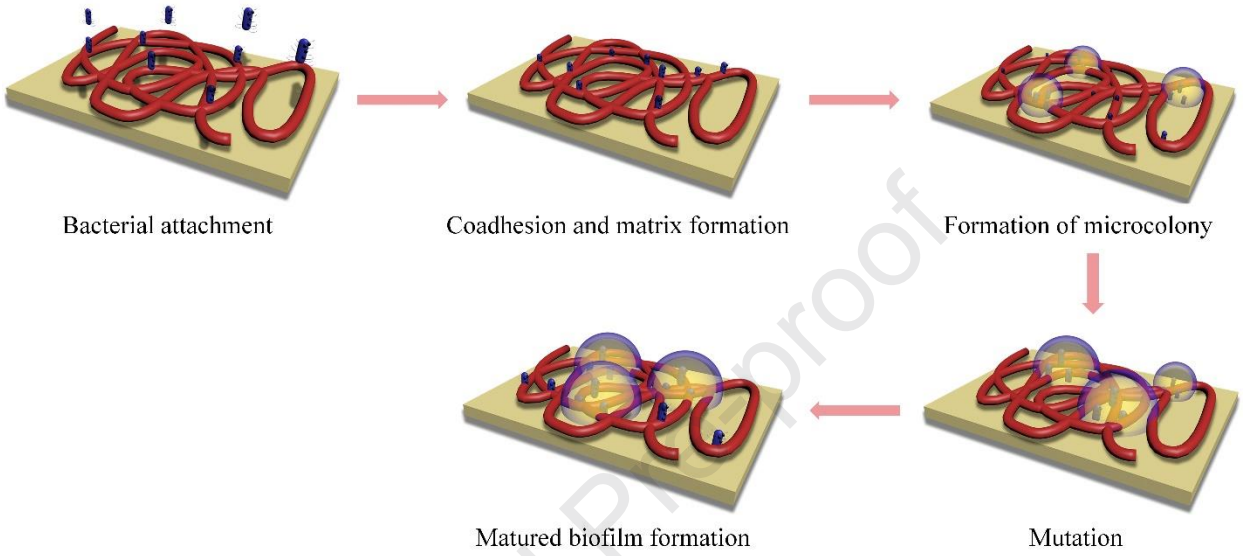


Figure 1. Schematic showing the development of a mature biofilm. Adapted with the permission from [18].

Biofilms shield singular cells from hostile factors like antimicrobial agents, supplemental limitations, and immunologic protection frameworks. Cells in a biofilm are contrasted in their genotypic and phenotypic expression from those of freely the suspended cells and these distinctions make them firmly resistant to antibiotics [19]. Aside from the immunity presented by the matrix, microbes in biofilms can utilize other survival mechanisms to dodge the host immune systems. These microbes can remain dormant and hidden from immune system and cause local tissue harm, which may later lead to acute infection. Inside a biofilm, the microscopic organisms can adjust to an absence of oxygen environment (anoxia) and supplement limitation by displaying altered metabolism, protein production, and gene expression, which may lead to lower the

metabolic rates and diminish the rates of cell division. These transformations make the microbes more resistant to antimicrobial treatments by reducing the requirements for cellular functions that the antimicrobials meddle with or by inactivating the antimicrobial targets. Synchronous enactment of both natural and acquired immune responses in the host may happen during the biofilm contamination. Neither of them can kill the biofilm organism. Instead, they cause a definitive increase in the collateral tissue damage. In this way, the diseases related with biofilms are extremely persistent diseases grow gradually, rarely get resolved by the host's immune system, and respond inconsistently to antimicrobial treatments [20]. In fact, they are more challenging than the planktonic cells and have turned into a major cause of deaths around the world. Predoi et al. [21] used chemical co-precipitation method to produce cerium doped hydroxyapatite (Ce-HAp) powder $Ca_{10-x}Ce_x(PO_4)_6(OH)_2$ coatings with x = 0.05 (5Ce-HAp). The results of the antimicrobial experiments demonstrated that the examined microbial strains of *E. coli* were successfully prevented from forming colonies using 5Ce-HAp coatings and solutions.

The simplest biofilm preventive measures have aimed to eliminate adhering microbes (antimicrobial) or to prevent microbial adhesion (antifouling). The excessive use of the antibiotics has led to the development of several pathogens that are resistant to antibiotics. Thus, antimicrobial therapy is becoming an increasingly challenging task to counter the contamination and infection. Hence, alternative strategies need to come up to tackle these problems.

3. Antibacterial surfaces for biomedical and healthcare settings

Desired biomaterials should possess certain biological properties that are related to the surface characteristics like biocompatibility, biodegradability, non-cytotoxic and anti-infective properties. The conventional understanding of surface interaction of bacterial pathogens can significantly affect the development of novel biomaterial-based implants. Bacterial cell adhesion and

proliferation can be controlled by engineering their surface properties. To prevent the development of biofilms on the surfaces of biomaterials, a surface must be capable of preventing bacteria's initial adhesion, eliminating any bacteria that have managed to penetrate the anti-adhesion barrier, and removing any dead bacteria that is present over the surface. It is crucial to comprehend the formation of these biofilms in detail. Excellent substrates for bacterial adhesion, colonization, and ultimately the biofilm formation are the biomaterials with coarse or permeable surfaces. **Figure 2** illustrates the cicada **(2a)** and dragonfly **(2b and 2c)** wings in which an individual gram-negative bacteria (*P. aeruginosa, B. catarrhalis, E. coli, and P fluorescens*) have been observed to sink and spread between nanopillars of the wing surfaces. Cell susceptibility did not appear to be influenced by the shape of the cells. The physical nanoprotrusions on the wing surface can harm and stretch microbial cells, which causes them to lyse and die [22][23][24]. This can give rise to the attachment and mechanical rupture of the bacterial cell wall, resulting in cell death within 20 minutes[25]. Dragonfly wings have also been found to fight gram-negative and gram-positive bacteria. The capillary design of the dragonfly wing nanoprotrusions causes increased cell wall stress and deformation, resulting the cell wall rupture and subsequent cytosol fluid leakage as shown in the areas marked with red color of **figure 2c.** To demonstrate the surface interaction, a typical (cicada wing) spatiotemporal 3D model for nanopillar and bacterial cell interaction is presented in **figure 2d.**

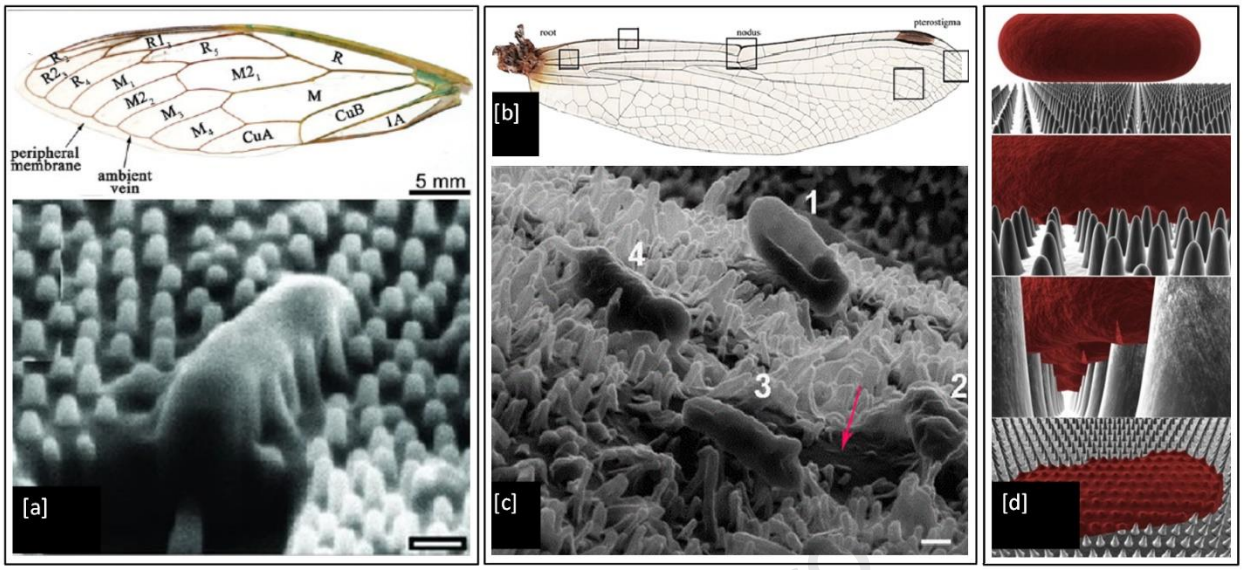


Figure 2. (a) Cicada forewing structural physiology and SEM image of a *P. aeruginosa* cell sliding between the nanopillars on the wing surface, (b) Common sand dragonfly wing images from optical microscope, (c) *E. coli* bacteria captured by SEM adhering to a dragonfly wing's uncoated nanopillar surface in various stages (the bacteria attachment are marked by numbers 1, 2, 3 and 4) of death, with a red arrow highlighting the darker portion induced by cellular extravasation overflowing the nanopillars, and (d) 3D spatiotemporal model of cicada wing nanopillar interactions with rod-shaped bacterial cells. Adapted with the permission from [26]**.**

Based on a near-infrared (NIR)-responsive organic/inorganic hybrid coating made up of gold nanorods and polyethylene glycol (PEG), Zhao et al. [27] developed a functionalized polyurethane surface (PU-Au-PEG) with antifouling and photothermal bactericidal capabilities. Under 808 nm NIR irradiation, the PU-Au-PEG demonstrated significant photothermal bactericidal capabilities, particularly against the multidrug-resistant bacteria, and demonstrated a high efficiency to resist the bacterial adhesion. Superhydrophobic surfaces can maintain optimum air pockets in microstructures to reduce the amount of water droplet contact with the materials and avoid microbial contamination[28]. Strong interactions between hydrophilic materials on the water and

the surface results in the formation of super hydrophilic anti-adhesion surfaces. Most antibacterial surfaces perform two or more functions simultaneously killing and resistance or release. However, the bacterial resistance and biocompatibility frequently conflict with one another. Therefore, it is necessary to improve the composition of the surface to achieve an optimal performance. To induce the bacterial release, most antibacterial surfaces use non-specific external stimuli (including temperature, light, and salt ions)[29]. It is necessary to focus on the development of antibacterial surfaces with self-stimulating capability by using endogenous triggers with biological specificity to boost the material surface efficiency. Chemical modification drives most of the bactericidal strategies. On the other hand, regulating bacterial adhesion also depends on the inclusion of surface microscale topographical factors. By manipulating the surface topography, surface chemistries, and mechanical properties, polymers with multiple length scales can be combined into various molecular and supramolecular structures, leading to the production of antimicrobial surfaces that can be used in a range of biomedical applications [30]. In accordance with how the bacteria are eradicated, bactericidal surfaces can be divided into two categories: contact-based surfaces and release-based surfaces. Recently, the antibacterial surface with dual functionality has received a lot of attention. Antibacterial coatings may reduce bacterial colonization and as a result the frequency of healthcare-associated infections could be minimized. Antibacterial coatings either limit the growth of bacteria through antifouling coatings or eliminate the bacteria that are already adhered to the surface with the help of bactericidal coatings. Any bacteria that can adhere to an antifouling coating will grow, but on the surfaces with bactericidal coatings, the accumulation of dead bacteria and other debris leaves the room for new microorganisms to colonize [31]. It is crucial to design an antibacterial coating specifically for the application for which it is intended, both in terms of the coating's effectiveness and durability over the intended period of application.

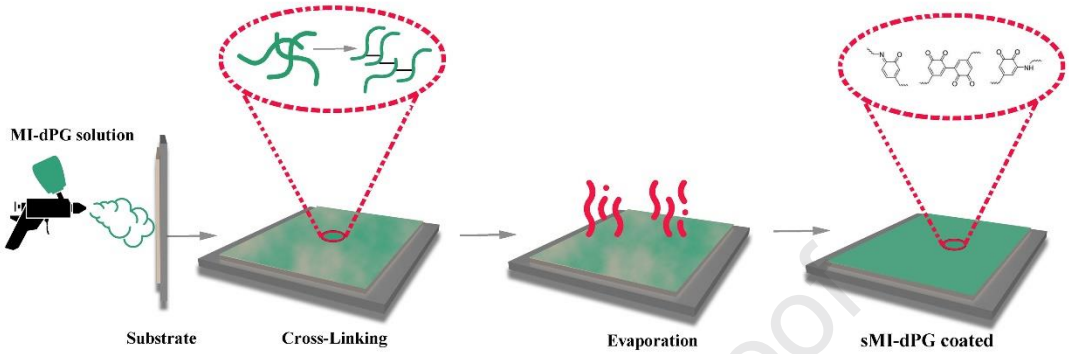
For instance, orthopedic implant's osseointegration may be severely impacted by the antifouling coatings, and high concentrations of cationic bactericidal polymers that may cause the hemolysis and platelet activation in a blood-contacting environment[32]. It is reasonable to assume that various biomedical applications will necessitate differing ideal ratios of bactericidal and antifouling components in the coating in order to achieve a high performance.

3. Science based strategies for antibacterial surface

3.1 Functionalized polymers as surface coatings

Bacterial adhesion and colonization take place when the surface of the implants is covered by the proteins adsorbed on to their surfaces. The antibacterial surface can be optimized by implementing the antifouling properties that repel these proteins from the surfaces. Clinical contaminants present one of the main impediments related to the implantation of any biomaterial after a medical procedure. Chua et al. [33] explored the utilization of polyelectrolyte multilayers (PEMs) involving hyaluronic acid (HA) and chitosan (CH) to give antibacterial properties on titanium (Ti) substrate. Yazici et al. [34] designed an engineered chimeric peptides with freely displayed antimicrobial domains as an antibacterial surface for application in orthopedic implants. Christoph et al. [35] developed a mussel polymer-based substrate-independent spray coating method for modifying the substrate using mussel-inspired dendritic polyglycerol (MI-dPG). This is a straightforward strategy for setting up a superhydrophobic, water-repellent coating by coformulation of the mussel-inspired spray coating with hydrophobic nanoparticles. Silver nanoparticles (AgNPs) were embedded on to the surface via a post-functionalization technique to boost the antibacterial properties. Wang et al. [36] developed a functional polyurethane composition (UP-C12-50-T) using the blend of hybrid soft block polyurethane and a traditional biomedical grade polyurethane (Tecoflex). Human mesenchymal stem cell (MSC) growth next to

221 and under UP-C12-50-T-10 revealed an outstanding biocompatibility and antibacterial properties
222 with *E. coli* and *S. epidermidis*.



223

224 **Figure 3**. Schematic representation of the mussel-inspired dendritic polyglycerol (MI-dPG) spray
225 coating. Adapted with the permission from [35].

226 Like the regular proteins, the synergistic impact of the catechol and amine functionalities
227 is also liable for solid attachment to the substrate (**Figure 3**). The multivalent and dendritic
228 polyglycerol platform of the MI-dPG upgrades the surface after crosslinking of the coating and
229 proves as an important coating technology to fight against the implant-related infection [37]. Due
230 to its high corrosion resistance, mechanical strength, and good biocompatibility, Ti is generally
231 used in orthopedic and dentistry implant prostheses [38]. However, the protein adsorption and
232 bacterial fouling post implantation are some of the issues of these implants. The bacterial fouling
233 on a superficial level of implants might cause critical problems and makes the bacterial panels
234 tolerant [39]. Therefore, in order to prevent the biofilm development and bacterial fouling on Ti-
235 based implantable clinical devices, several procedures are implemented [40]. Several antibacterial
236 coatings have been accounted for by utilizing the antimicrobial silver [41], peptides [42],
237 photodynamic agents [43], and cationic polymers [44].

238 The surfaces with unique properties such as superhydrophilicity or super hydrophobicity
239 display microbial resistance through their antifouling component. Generally, a boundary is created
240 between these surfaces to block direct contact between the surfaces and the microbes.
241 Superhydrophilicity can be accomplished by covering the surface using nanostructures or covering
242 of hydrophobic surfaces with a hydrophilic material [45]. The hydrophobic nature of certain
243 polymers like polycaprolactone (PCL), Poly(lactic acid) (PLA), polystyrene (PS), which are
244 exposed with organic frameworks, have shown high vulnerability for bacterial biofilm
245 development. The hydrophobicity of these polymer surfaces are adjusted by different surface
246 modifications techniques, like chemical etching, acid treatment, leaching, and others to overcome
247 the bacterial adhesion [46].

248 **3.2 Composite films with antimicrobial nanoparticles**

249 Antibacterial nanoparticles are the materials with an inbuilt capability of fighting against microbes.
250 These nanoparticles are used as various carriers for other biocidal agents [47]. The benefits of
251 these nanoparticles are higher surface-to-volume ratio which can maintain optimized antibacterial
252 efficacy because of their ultra-size and the possibility to functionalize with various other
253 biomolecules [48]. The nanoparticles are proved to offer antimicrobial properties to various
254 biomedical implants, some of the mechanisms such as reactive oxygen species (ROS) , dissolved
255 metal ions, physical interaction, internalization into the cells are shown in **figure 4** [49].

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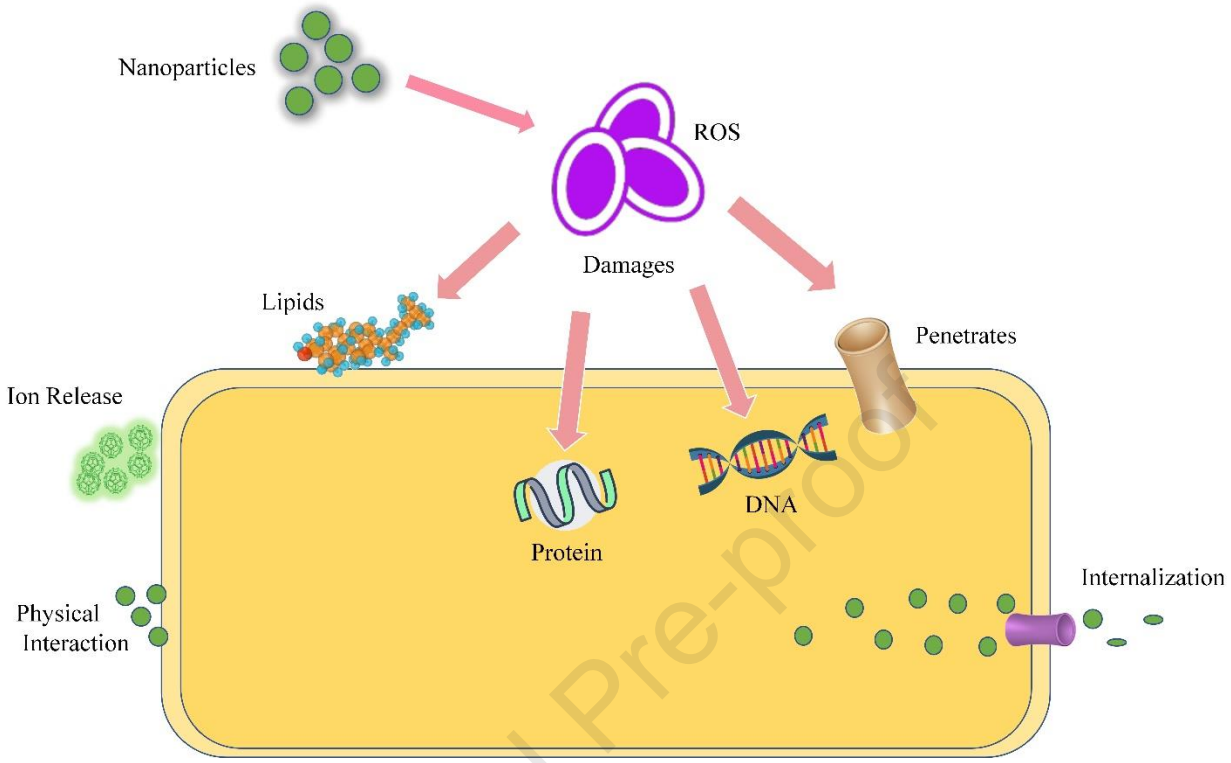

Figure 4 The mechanism of action of antibacterial metal nanoparticles in a composite film. Adapted with the permission from [49]

These nanoparticles do not act like standard antibiotics. Instead, they directly trigger the responses that create a communication with the cell wall of bacteria pertaining to the prevention of biofilm formation[50]. The AgNPs are viewed as one of the best antibacterial agents amongst the metal nanoparticles[51]. The cell membrane disruption of the bacterial cells is caused by the adsorption of AgNPs leading to a depolarization of the bacterial cell wall. ATP production and DNA replication are hindered by the ROS generated by the infiltration of AgNPs**.** [52].

Composite films with AgNPs could offer an excellent antibacterial property to the surface. Favia et al. [53] considered the plasma-deposition of silver containing polyethyleneoxide (PEO)-like coatings as an antibacterial surface. Actinometry revealed a correlation between the amount

of silver (Ag) embedded in the coatings and sputtered in the discharge, which could be used to control the in situ deposition. By spray-coating hydrophobic silica sol and copper oxide (CuO) nanoparticles, Ren et al. [54] developed a transparent and superhydrophobic bactericidal coating. The superhydrophobic properties of the formulation prevented *Escherichia coli and E. coli* from adhering to it by up to 3.2 log cells/cm^2 as compared to a bare glass. Furthermore, the live/dead staining results demonstrated that the coating's performance against *E. coli* was outstanding when applied as prepared. Zaporojtchenko et al. [55] used co-sputtering of noble metals with polytetrafluorethylene (PTFE) to create antibacterial metal/polymer nanocomposite coating with thin metallic rich surface layer. The *S. aureus* and *S. epidermidis* were utilized as test microbes for evaluation of antibacterial efficacy of these surfaces. 1% of gold (Au) could substantially increase the release rate of Ag^+ ions. Ag is more dynamic than Au, and the presence of Au improves Ag^+ particle arrangement. The functional parameters such as power, and pressure applied to the magnetrons control the properties of the nanocomposite films. Beier et al. [56] used atmospheric pressure plasma chemical vapor deposition (APCVD) to synthesize the antibacterial thin films. The results of antibacterial test using *E. coli* showed that the coatings could have an excellent antibacterial effect. In a study employing APCVD and sol-gel technology, Gerullis et al. [57] examined the structural morphology, elemental composition, and antibacterial characteristics of zink (Zn), Ag and Cu incorporated thin silicon oxide (SiO_2) films deposited on wood polymer composites (WPC). BacTiter-Glo® tests revealed that Zn), Ag and Cu-containing layers had substantial bactericidal effects against *E. coli*. Dudek et al. [58] introduced a method to enhance the antibacterial performance of the Nickel-titanium (NiTi) alloy to prolong its effectiveness for healthcare application. The colloidal suspension of 450nm particle size of tricalcium phosphate (TCP) and the Ag/SiO_2 nanocomposite could produce structurally distinctive calcium

phosphosilicate coating via electrophoretic deposition (EPD). Deng et al. [59] demonstrated a single-step fabrication of antibacterial nanocomposite thin film with imbedded AgNPs. The APCVD technique was used to feed AgNPs directly into the discharge zone. Antibacterial tests over these films using *E. coli* and *S. aureus* demonstrated an excellent antibacterial property and the method can be used to overcome the issues of device related contamination. Wiesenmueller et al. [60] developed a method to create a cytocompatible and antibacterial coating with long-term antibacterial effect. The results indicated the tunable release of Ag is necessary to maintain appropriate cytocompatibility and superior antibacterial activity of the modified surface. Ag-free top layer was deposited on an Ag-rich base layer, which resulted a better control over Ag^+ release behavior. Here, the Ag-rich layer serves as an Ag-repository and the burst-release of Ag^+ ions from the Ag-reservoir is prevented by the top layer that acts as a diffusion barrier. The nanocomposite films were tested using NIH3T3 mammalian cell line as well as Gram-negative (*P. aeruginosa*) and Gram-positive (*S. aureus*) bacterial strains. The results demonstrated a tunable and log-term antimicrobial activity of the films, while retaining an appropriate cytocompatibility over testing duration. Pollini et al. [61] introduced stereolithographic synthesis of antimicrobial composites made of HAp for dental applications. Up to 5% filler content resulted in an increase in flexural strength of the composites. In comparison to the neat samples, the inclusion of uniformly distributed commercial HAp decreased the bacterial (*S. aureus*, *Escherichia coli)* and fungal (*C. albicans*) growth in a dose-dependent manner. Nataliya et al. [62] used wet chemical method to generate gelatin nanofibers (GNF) with zinc oxide (ZnO) composites (GNF@ZnO composites). The GNF@ZnO composites demonstrated antibacterial activity against *P. fluorescence* and *S. aureus.*

315 The intrinsic antibacterial properties of metal and metal oxide nanoparticles could be used
316 to control the bactericidal effectiveness of the composite films. These composite films with
317 nanobiocides could be used for implant or catheter coatings and wound dressings for controlling
318 the bacterial infection.

319 **3.3 Antibacterial surfaces through plasma surface modification**

320 Low temperature plasma (LTP) is a quick and effective disinfection method unrestricted by
321 bacterial resistance mechanisms. Hence, it offers a novel approach to overcome the medication
322 resistance. Using LTP surface modification technique, antibacterial surface and coating have been
323 developed in a number of ways [63]. The plasma surface treatment creates the surface
324 functionalities (anchoring sites for loading various antimicrobials) and subsequent grafting of anti-
325 bacterial polymers/peptides. The design and creation of such surfaces that either prevent bacterial
326 adhesion or resist biofilm formation are the major research strategies. The surface functionalization
327 using ammonia plasma or amine plasma are considered as the most appropriate plasma surface
328 treatment strategies, which are quite like cationic disinfectants (contact-killing by forming
329 quaternary ammonium salts). The plasma surface modification has been extensively studied for
330 engineering anti-biofouling surfaces. Further, for some of the polymers, the shelf-life of plasma
331 modified surface is restricted by the issue of surface ageing (hydrophobic recuperation) after
332 plasma treatment [64]. The deposition of antibacterial nanocomposite films on a surface can
333 generate the desired antimicrobial activity. Generally, in these films (polymer matrix filled with
334 the nanoparticles) can be prepared utilizing the plasma-sputtering of a bulk metal to directly
335 incorporate the nanoparticles into the polymer [65]. The plasma electrolytic oxidation of metal
336 implants and plasma enhanced reduction of metals (Ag, Au, Cu etc.) directly onto polymer

membranes were reported by our collaborative team at UAB [66]. The common plasma process methodology of different biomaterial surface is shown in the **figure 5.**

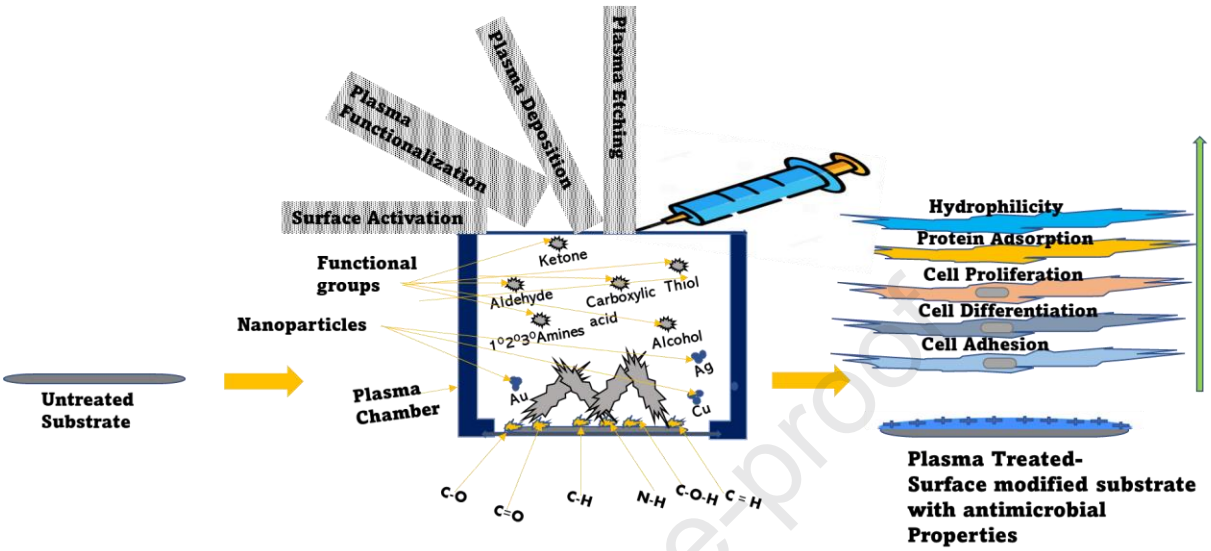

Figure 5: Surface activation of biomaterials through plasma and impact of modified surface to cell behavior [67]

In recent years, plasma surface modification technologies have been used as a tool to create a variety of antibacterial surfaces. Despax et al. [68] investigated Ag-containing plasma polymerized siloxane films. The hexamethyldisiloxane (HMDSO) mass stream rate was used to screen the balance between the Ag sputtering and plasma polymerization. Under various plasma process conditions, the nanocomposite films had their Ag content ranging from 0-32.5%. Peter et al. [69] developed nanocomposite materials with an Ag nanocluster and a SiOxCyHz-polymer matrix. A gas aggregation cluster source (GAS) could produce Ag nanoclusters with sizes ranging from 2-20 nm, and typically it could deposit them quickly through a concentrated pulse. In order to incorporate antibacterial characteristics, Spange et al.[70] functionalized the wound dressings employing APCVD method. The functionalized dressings demonstrated a very strong antibacterial effect against *S. aureus* and *K. pneumoniae*, via direct contact killing mechanism. Kuzminova et

al. [71] fabricated silver nanoparticle-based antibacterial nanocomposite coatings using GAS of AgNPs and plasma enhanced-CVD (PECVD) of the matrix material. The quantity of AgNPs as well as matrix material characteristics (chemical composition or wettability) could be modulated when GAS and PECVD were used. This further impacts the Ag^+ release kinetics, which determines how effectively the composites kill the microbes. Blanchard et al. [72] developed plasma-polymerized HMDSO (ppHMDSO) film in which the retention of carbon groups is reduced by the addition of oxygen (O_2), resulting the formation of a more inorganic, hydrophilic ppSiOx film. The developed films could be investigated for their antibacterial properties. Deng et al. [73] [74] developed the method to deposit AgNPs over the polyethylene terephthalate (PET) matrix using the air pressure deposition method. AgNPs could be uniformly immobilized on the PET surface and the thickness of the deposition could control the release of AgNPs and the antibacterial properties of the PET film.

3.4 Plasma-assisted surface grafting of antibacterial components

LTP could be used as a pre-treatment step to modify the material or fabric surfaces for subsequent grafting. Chang et al. [75] used plasma pre-treatment to accelerate chitosan grafting on polyester surfaces. The textures were first activated on the surface using argon/oxygen (Ar/O_2) dielectric barrier discharge (DBD) plasma before being exposed to the atmosphere for oxidation. The fabrics were immersed in chitosan solvent for chitosan grafting. The grafted surface exhibited a better biocompatibility with fibroblast cells and antibacterial efficacy against *B. subtilis and S. aureus.* Karam et al. [76] altered the polyethylene by using Ar/O_2 plasma, nitrogen (N_2) plasma and plasma-induced grafting of acrylic acid (AA) to examine the determining factors for adsorption. As a reactive layer for the immobilization of antibacterial nisin peptide on steel surfaces, Duday et al. [77] utilized the plasma polymerized organosilicon coatings to create antibacterial Ag-

stacked cotton/polyester textures. Kostic et al. [78] treated the raw fabrics with air DBD plasma prior to submerge in an aqueous silver nitrate ($AgNO_3$) solution. The fabric could absorb Ag^+ to its surface and the adsorption to the textures was impacted by the treatment time and aging time. In addition to the utilization of plasma-engineered surfaces for antibacterial strategies (bactericidal-agent release surfaces, contact-killing surfaces, and anti-biofouling surfaces), plasma-active antibacterial surfaces are gaining much attention due to the emergence of portable cold atmospheric plasma systems [79]. In order to treat chronic wounds, Boekema et al. [80] created an atmospheric pressure surface plasma generator and established it's *in vitro* and *in vivo* reliability and efficacy in bacterial cell reduction (**Figure 6).**

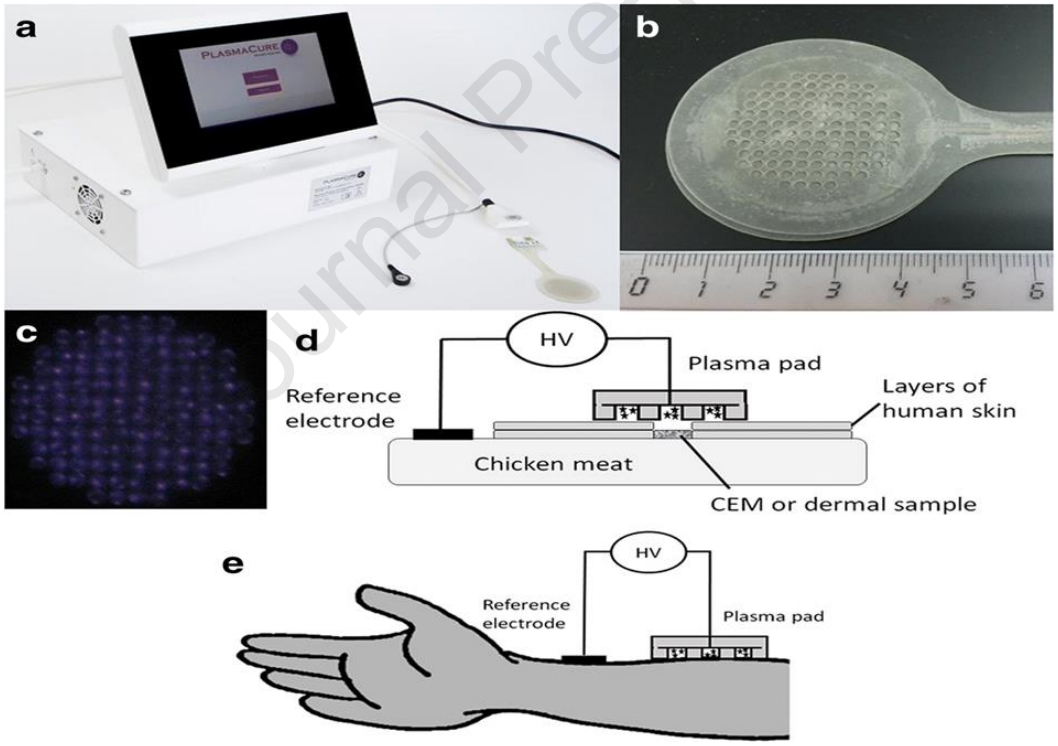

Figure 6. Antibacterial and safety test of a flexible cold atmospheric plasma device for chronic wound healing. **a.** The plasma device consisting of the plasma driving unit (plasma pulser) and plasma pad; **b.** plasma pad with scale in cm. Plasma pad showing the side with prefabricated holes

that is in contact with the skin; **c.** plasma is generated in the small holes; **d.** schematic diagram of device for the treatment of samples on chicken meat as a support layer; layers of human skin (0.7 mm) were used to increase the distance between sample and plasma; **e**. schematic diagram of device (HV: high voltage; CEM: collagen elastin matrix). (Adapted from [80])

4. Conclusion and future scope

The engineered strategies for creating an antibacterial surface with bactericidal properties using functionalized polymeric coatings, nanoparticle and plasma-based surface modification are discussed. It is witnessed in most of the developments that the biofilm development may be restricted by restraining introductory attachment of the bacteria. The current research endeavors are coordinated towards the killing or diminishing bacterial colonies on implants and medical devices through the bactericidal properties of the surface. It is important to note that antibacterial agent release in general, are neither a remedy nor a guaranteed method. Instead, they need to be considered carefully as a component of a coordinated effort to reduce established risk factors for pathogenic bacteria. However, several significant obstacles need to be addressed before release-based coatings can be effectively used to combat the infections. The duration and kinetics of antibacterial administration varies depending on the application. First- or second-order kinetics govern the typical release patterns that are in use today, which typically involve an initial release followed by a decreasing downstream dispersion that lasts anywhere from a few hours to several days. An antibacterial antibiotic that releases quickly and in a high dose could initially seem favorable. It offers antibacterial defense throughout the early postoperative period, which is thought to pose the greatest risk of infection and prevents bacterial resistance emergence. The long-term release is often required in cases of revision or second surgery, as the tissues around the primary implant are regularly contaminated. Currently, it is extremely difficult to create the

coatings that keep released antibacterial component levels within the therapeutic window, sufficient to kill bacteria but low enough to prevent harm to eukaryotes. Therefore, creative methods are required to manage and expand the release kinetics to provide new products or services. Although, there have been many documented antibacterial techniques in the literature, only a limited platforms have reached clinical testing and use. The inadequacy of realistic *in vivo* settings in most of the current *in vitro* testing protocols for antibacterial materials is still a crucial factor responsible for the failure of translational success. The current status and the future challenges presented in this review will assist the researchers to foster the study and development of advanced antibacterial coatings for biomedical and clinical settings.

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Author contributions

All the authors listed have made a substantial, direct, and intellectual contribution to the work and approved for its publication.

Conflict of Interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Declaration of interests

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

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: