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Nanoparticles at biointerfaces: Antibacterial activity and nanotoxicology

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ABSTRACT

Development of a biomaterial that is resistant to the adhesion and consequential proliferation of bacteria, represents a significant challenge in terms of application of such materials in various aspects of health care. Over recent years a large number of synthetic methods have appeared with the overall goal of the prevention of bacterial adhesion to surfaces. In contrast to these artificial techniques, living organisms over millions of years have developed different systems to prevent the colonization of microorganisms. Recently, these natural approaches, which are based on surface nanotopography, have been mimicked to fabricate a modern antibacterial surface. In this vein, use of nanoparticle (NP) technology has been explored in order to create a suitable antibacterial surface. However, few studies have focused on the toxicity of these techniques and the ecotoxicity of NP materials on mammalian and bacterial cells simultaneously. Researchers have observed that the majority of previous studies have demonstrated some of the extents of the harmful impacts on mammalian cells. Here, we provide a critical review of the NP approach to antibacterial surface treatment, and also summarize the studies of toxic effects caused by metal NPs on bacteria and mammalian cells.

1. Introduction

Some of the oldest living creatures on the earth are microorganisms [1]. They have evolved versatile mechanisms for the colonization of different surfaces over the millions of years of their existence [2]. As one of the oldest microorganisms, the bacterium is found almost everywhere possible on Earth [3]. Bacteria can adhere to different surfaces and by reproduction and proliferation will form dense structures, usually termed "biofilms", with thicknesses varying from micrometers to half a meter [4]. In 1935, Zobell and Allen [5] reported the first study focusing on bacterial adherence on a solid substrate. Since then, studies of bacterial adherence have been performed on a variety of natural and artificial substrates [6–9]. The first bacterial adherent layer to a surface is created by physical effects, such as thermal, hydrodynamic and van der Waals forces, electrostatic and hydrophobic interactions, and steric hindrances [10]. Subsequent to this process, a second layer is created by special bacteria adhesins that are induced by specific receptor ligands which are located on the bacterial cell. These species facilitate bacteria in order to have an irreversible matrix and biofilm growth on the surface, which is named the extracellular polymeric substance (EPS) [11,12]. The group of bacterial cells attached to a substrate within the EPS is what is actually referred to as a biofilm. This structure is responsible for infections associated with the surfaces of medical devices such as catheters [13]. Biofilms generally form mushroom-like structures [14,15]. Various steps lead to the formation of a biofilm, of which the three major characterized stages are: (i) attachment, (ii) growth and (iii) detachment. Notably, within such films, bacterial cells are less sensitive to the action of antibiotics. Consequently, the formation of biofilms is a major concern in the biomedical devices field [16,17].

In order to mitigate the impact caused by biofilms in various fields, there have been numerous efforts to develop antibacterial surfaces which may prevent the initial formation of inactivated cells coming into contact with the substrate. These surfaces can be categorized as antibiofouling and bactericidal [3,12]. In this regard, it is noteworthy that a number of antibacterial surfaces may possess both functions [1]. Antibiofouling describes surfaces which may resist or repel bacterial adherence due to undesirable physical or chemical surface conditions in terms of an environment for bacterial growth [18]. Bactericidal surfaces kill the cell in contact through the chemical reactions between the surface and the cell membrane [1,19].

A significant amount of research has been focused on types of surfaces that are capable of the prevention of biofilm formation [20–22], including those having their origin in natural processes. With respect to the latter, it is essential to minimize dust and bacteria attachment to insects in order to maintain their biological functionality [18].

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Consequently, certain insects through evolution have developed various methods or mechanisms to manage the impact of particulate matter [23]. One of the frequent mechanisms evident for insects is the presence of super-hydrophobic wings. This mechanism not only relies on the minimization of the weight and any moisture on the wings but also depends on its self-cleaning effect, which immunizes the insect against infection [24]. In this case, droplets of water which contact the surface can easily slide from the wing, resulting in the removal of particles [21]. Accordingly, it is very likely that there exists a direct connection between antibacterial capability and self-cleaning [25]. There are several other examples of natural antibacterial surfaces, including lotus leaves (*Nelumbo nucifera*) [26], shark skin (*Mako shark*) [27], and the feet of geckos [28]. Additionally, insect such as cicadae [20,21,25,29], dragonflies [21], and butterflies [30] are further examples that have super-hydrophobic wing surfaces with antibacterial capability. The best paradigm for biomaterials that can remove bacteria in contact is the Clanger cicada (*Psaltoda claripennis*) wings [31]. This species possesses a remarkable nanopattern topography (nanopillars) on surfaces of its wings which confer an environment unfavorable for bacterial adhesion [21]. Importantly, such a structure leads those concerned with antimicrobial surface chemistry to a possible "synthetic" solution to the adherence problem (Fig. 1). A specialized derivative of the nanopattern concept is the NP, which is the main focus of the present Review.

Nanoparticles (NPs) are materials which have at least one dimension in the nanoscale range (< 100 nm). The NPs have been widely used for the delivery of antibiotics and the treatment of infectious diseases [32], and in medical sensing, targeted drug delivery, and artificial implants [33]. In addition to these applications, various reports on the employment of NPs for the development of antibacterial surfaces have appeared. The main reason for this is due to their high surface-area-to-volume ratio which causes such particles to have physical and chemical properties that are different from those of their bulk materials [34,35]. In this regard, metallic silver, zinc oxide, and titanium dioxide NPs have been used extensively in the quest for fabrication of antibacterial surfaces [36–41].

The employment of NPs to produce antimicrobial effects on surfaces has taken place in many different efforts. Over the past few decades, several surface modification or treatment methods have been used for fabrication of efficient antibacterial surfaces [42,43]. These fabrication methods can be classified as being surface functionalization, derivatization, polymerization, or mechanical or surface architecture modification. The first three techniques mostly focus on the chemical modification of the surface. Also, surface structuring and/or mechanical approaches are considered to be a physicomechanical modification of the surfaces [1]. For the fabrication of artificial antibacterial surfaces, several traditional and advanced surface modification techniques have been used [25–27]. Some of these artificial surfaces have exhibited bactericidal and/or antibiofouling effects. However, one of the major challenges, which still remains in this area, is finding optimal fabrication techniques to create an efficient antibacterial surface. Surface nanotopography is one of the highly promising fabrication methods in this area [25,44]. Based on a previous study, in which researchers addressed an efficient fabrication method [25], surface nanotopography confers a promising ability to create a suitable antibacterial surface.

One of the main challenges is that even though information concerning the antibacterial capability of NPs (metal oxide) continues to increase, a significant lack of information still remains in order to elucidate the toxicity of such particles [45]. It is clear that in light of the rapid expansion of antibacterial surfaces, the toxicity of such surfaces, especially those involving NPs, represents a potentially serious issue in terms of future medical applications. The latter area is termed "nanotoxicology" and its importance is now recognized via the relatively recent appearance of several journals focusing on the topic (Table 1). This review provides an overview of the technology of antibacterial surfaces, various fabrication methods, and a summary of existing challenges, especially those associated with the nanotoxicological aspects of the antibacterial surfaces.

2. The bacterium-material interaction

2.1. Surface nanotopography and nanostructuring

Although the main focus of past studies has been the investigation of interactions between bacteria and antibacterial surfaces, including

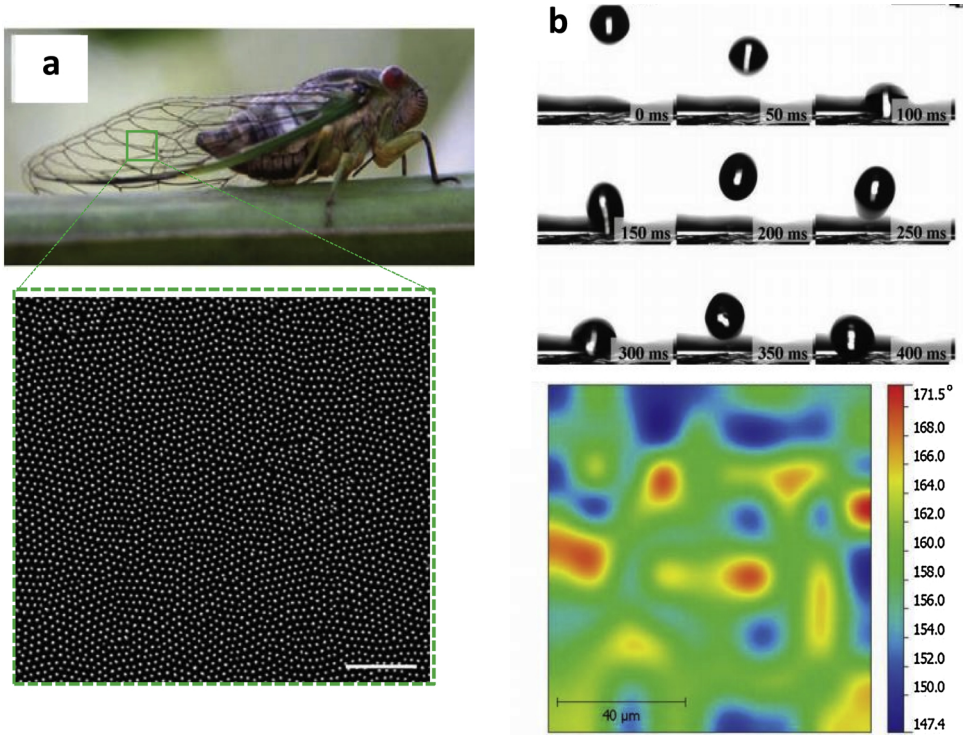

Fig. 1. nanopattern topography and antibacterial capability of animal wings. a) Photograph of cicada, *Psaltoda claripenni.* [21]) SEM image of the cicada wing surface, at 25,000× magnification. The surface consists of an array of nanoscale pillars (Scale bar is 2 µm) b) A water droplet contacting the wing surface. When the droplet contacts the wing, the superhydrophobic surface cause repellent, and the droplet bounce. [21] and the wettability map of the wing surface constructed from the repeated measurement of static water contact angle in an array of positions. Contact angles were measured at 10 µm intervals and were found to range between 147° and 172°. The color scale indicates the contact angle (in degrees). *"Adapted with permission from E. P. Ivanova, J. Hasan, H. K. Webb, V. K. Truong, G. S. Watson, J. A. Watson, V. A. Baulin, S. Pogodin, J. Y. Wang, M. J. Tobin, C. Löbbe, R. J. Crawford, Small 2012, Copyright (2019) John Wiley and Sons"* [21].

Table 1
Nanotoxicology – example Special Issues and Journals since 2010.

Publication vehicle	Publisher	Type
Journal of Nanobiotechnology	BMC, Springer Nature	Journal
Nanotoxicology	Taylor and Francis	Journal
J. of Nanotoxicology and Nanomedicine	IGI Global	Journal
Nanotoxicology	Informa Health Care	Journal
ACSNano	ACS	Virtual issue 4, 2010
Archives of Toxicology	Springer	Special issue 85, 2011
Nature Nanotechnology	Nature Publ. Group	Special issue On-line 2011
Small	Wiley	Special issue 9, 2013
Nanomaterials	MDPI	Special issue 4, 2014
Angewandte Chemie	Wiley-VCH	Special issue 53, 2014
Nanotoxicology	RSC	Web-themed collection 2015
Intl. J. of Molecular Sciences	MDPI	Special issue 19, 2018
Ecotoxicology and Safety and Environmental	ELSEVIER	Virtual issue 2019

chemical reactions at interfaces that repel the bacteria cells to form the biofilm [13], there are a few reports that describe the examination of the influence of surface topography on bacterial adhesion [45]. The discovery of the antibacterial capabilities of insect wings due to the array of nanopillars on the wing surfaces has stimulated the study of the surface nanotopography effect [46,47]. This finding has redefined previous topography concepts in order to fabricate a novel antibacterial surface [21,25]. Indeed, a number of recent reports have focused on designing and fabricating nanotopography-based antibacterial surfaces that not only resist adhesion but also kill the bacteria cells [48]. Thus, the number of antibacterial surfaces with nanoscale surface topography is growing rapidly [47]. Various fabrication methods such as nanoimprint lithography (NIL) and deep reactive ion etching (DRIE) have been shown to be promising techniques for construction of high-aspect-ratio nanostructured antibacterial surfaces [25]. The interactions of recently fabricated nanopattern surfaces with different types of the bacterium are shown in Table 2. In addition, a collection of previous results are presented in Fig. 2 [13,49].

2.2. Cell-surface interface dynamics

Over the past decades, researchers have attempted to understand the mechanisms of cell-surface interface dynamics. Despite this effort, much remains to be established [49]. Recently, the development of equipment has rendered it feasible to investigate various parameters (such as the mechanical, biological, chemical and physical) which affect the cell–surface interface dynamics [49]. Bacteria cell-surface adhesion is the major phase in settlement, proliferation, and biofilm formation. It has been shown that the fundamental behaviors of cells, including their selective attachment to a substrate surface, is clearly related to the properties of the biomaterial they attach to [50,51]. In the literature, several parameters have been reported to influence on cell-surface interface dynamics, such as the nature of the material (e.g., chemical structure, surface topography, and surface energy) and the specifications of the surrounding medium of the bacteria cells on the substrate [49]. This medium can increase or decrease bacterial cell adhesion, not only by changing the characteristics of the surface but also by applying different osmotic pressures to the bacterial cells. Various environmental factors also directly affect the cell-surface interface dynamics, such as temperature, nutrient availability, combination and concentration of harmful chemicals (e.g. antibacterial components and metal ions). For example, the liquid flow conditions which surround the bacterial cells can affect bacteria cell attachment to a surface and the probability of the bacterial cell detachment. Further examples are the acidity and ionic strength of the surrounding solution. Due to the electrostatic interactions involved in the biofilm structure, it has been found that ionic strength and acidity of the surrounding solution significantly impact the strength of hydrophobicity of the bacterial cell and abiotic target surfaces [49]. Consequently, cell-surface interface dynamics will intuitively influence various biofilm formation parameters, such as initiation, development, and stability. Other previous works have reviewed the role of bacteria cell interactions with substrates [52,53].

3. Fabrication methods

3.1. Synthesis of nanoparticles

Development of novel and efficient antibacterial agents, which can be used as an alternative to antibiotics, appears to be a vital topic in the antimicrobial field. Several types of metal and metal oxide nanoparticles have been acknowledged for their potential antibacterial properties, such as silver(Ag), titanium(Ti), silicon(Si), magnesium (Mg), copper(Cu), aluminum(Al), calcium (Ca), Y(yttrium) and their oxides [33,54,55]. Metal/polymer nanocomposites have been used widely in applications in environmental technology, electronics, optics, catalysis, and biotechnology [9–15,35]. Several techniques have been used to fabricate materials, such as intercalation, *in-situ* polymerization, sol-gel methodology, and direct mixing of polymer and nanofiller [35,56].

Silver, copper, and gold have been used mostly for the synthesis of stable dispersions of NPs in metal/polymer nanocomposites [57]. These particular nanocomposites have been used in a variety of fields such as biological labeling, optoelectronics, and surface-enhanced Raman scattering detection [35]. Notably, functionalized and biocompatible metal NPs in nanocomposites have seen successful applications in cancer detection and therapeutics [58]. This is especially the case for Au NPs, which have been employed extensively in clinical diagnostics and in drug delivery. For instance, colloidal gold is a promising candidate for targeted drug delivery approach, due to the distinctive chemical properties of gold NPs [59]. Recently, Yuan et al. proposed a promising recyclable nanocomposite using modified gold NPs which specifically inhibits *E. coli* cells [60].

Metal NPs exhibit the surface plasmon resonance (SPR) effect in the context of ultraviolet-visible spectroscopy. Hence, the synthesized metal NPs can be detected and measured with respect to particle shape, size, and inter-particle properties based on the change in the absorbance of wavelengths [61]. Researchers have revealed that the size, stability, physical and chemical properties of such particles depend on different parameters. The employed experimental conditions and the interaction kinematics of metal NPs are the main effective parameters [57]. Therefore, several chemical methods such electrochemical techniques, photochemical reduction and chemical reduction in addition to physical approaches have been used to stabilize metal NPs [61,62].

Table 2
Antibiofouling patterned surfaces reported recently.

Bacteria and their shape	Incubation time	Surface type	Surface features	Height	Width	Spacing	Observation
Staphylococcus aureus (Spherical)	Incubated for 1–4 hours	(a) Polystyrene, (b) polystyrene-b-poly (acrylic acid) (PS-b-PAA), (c) polystyrene-b-poly(L-glutamic acid) (PS-b-PGA) and (d) polystyrene-b-poly[poly (ethylene glycol)methyl ether methacrylate] (PS-b-PEGMA)	Open boxes Square shaped Crosshatched Pillars Lines Hexagon	200 (nm) 120 (nm) 140 (nm) 175 (nm) – –	20 (μm) 7.5, 19, 37 (μm) 20 (μm) 5 (μm) 22 (μm) 41 (μm)	5 (μm) 5, 6, 25 (μm) – 20 (μm) 40 (μm) 26 (μm)	Bacterial immobilization is favored by a PAA block copolymer. Different polymer blends provide insight into bacterial isolation and positioning. [108]
Staphylococcus aureus (Spherical)	Incubated for 0.5, 5.5 and 24 hours	PEG microgel and silanized glass slide	Circular pillars	90 (nm)	$\alpha = 1, 2, 3, 5$ (μm)	$\beta = \alpha/2, \alpha, 2\alpha$ (μm)	Attachment of an order of magnitude less than on the control; suggests a diameter of 2–5 μm and spacing of 1–2 times of the diameter for optimum biofilm inhibition and promoting tissue growth. [109]
Staphylococcus aureus and Staphylococcus epidermidis (Spherical)	Incubated for 1 and 18 hours	Thermoplastic polyurethane (TPU)	Sharklet micropattern	3 (μm)	2 (μm)	2 (μm)	In the range of environments selected to model the clinical environment, the-3SK2 × 2 TPU surfaces demonstrated significant reductions of S. aureus colonization ranging from 63% to 70% compared to unpatterned TPU controls [110]
Enterobacter cloacae (Rod-shaped)	Incubated for 48 hours	PDMS	Cross pillars Hexagonal pillars Hexagonal pits Sinusoidal Sharklet™	23, 9 (μm) 11 (μm) 7 (μm) 3 (μm)	21, 4 (μm) 3 (μm) 3 (μm) 4, 8, 2, 16 (μm)	5, 2 (μm) 2 (μm) 5 (μm) 2 (μm)	Bacterial cells attached to the walls and recessed regions between the patterns. Confirmed less attachment than the smooth PDMS control surface due to the less area fraction on patterned surfaces. [106]
Escherichia coli (Rod-shaped)	Incubated for 12 hours	Spinach leaves, PDMS and AGAR	Spatial symmetry of a natural surface	–	–	–	Bacterial cells aggregated in the valleys of the random topographical surfaces even after biocide treatment. [111]
Escherichia coli (Rod-shaped)	Tested under real-time flow conditions	PDMS	Wells	5(μm)	10(μm)	7(μm)	Dynamic stability of the bacterial cells depends on the surface topography and flow parameters. The cells swimming on patterned substrates experience a differential and complex environment. [112]
Escherichia coli (Rod-shaped)	Incubated for 18 hours	SiN-PMMA	Nanowire	44 (μm)	D = 100 nm	–	The released lysozyme molecules maintained their enzymatic activity and thus served as biocides to kill bacteria both suspended in solution and attached to the surface. [113]
Escherichia coli , Staphylococcus aureus and Helicobacter pylori (Rod shape and Spherical)	Incubated for 48 h	polyethylene terephthalate (PET)	Pillar-like	1000 (nm)	D = 250 nm	50, 200, 400 (nm)	The number of attached bacteria and the bacterial morphology, such as the diameter, length are affected by Increasing the interpillar spacing [114]

(*continued on next page*)

Table 2 (*continued*)

Bacteria and their shape	Incubation time	Surface type	Surface features	Height	Width	Spacing	Observation
Staphylococcus aureus (Spherical)	Incubated for 2 and 6 hours	Polystyrene	Line-like Pillar-like Complex lamella	1.6 1.8 0.471, 4.3 (μm)	1, 3, 5 1, 3, 5 2, 5 (μm)	– – –	In line- and pillar-like surfaces, spatial period of 1 μm had a greater degree of bacterial attachment than on spatial periods of 5 μm. Although, cells on lamella-like patterns were significantly reduced compared to smooth control surfaces. [115]
Staphylococcus aureus (Spherical) and Escherichia coli (Rod-shaped)	Incubated for 12 and 24 hours	Silicon wafer	Circular and square pillars	3(μm)	0.6, 0.8, 1, 1.2, 1.4, 2, 5, 10, 20(μm)	0.6, 0.8, 1, 1.2, 1.4, 2, 5, 10, 20(μm)	The microtopography patterned surface with equal width and spacing caused bacterial retention in comparison with smooth controls. E. coli adhered more on the 1.4–2 μm patterned surface while S. aureus adhered more on smooth controls. [116]
Staphylococcus aureus (Spherical), Escherichia coli (Rod shape), Staphylococcus epidermidis (Spherical), Shewanella oneidensis (Rod shape) and Pseudomonas aeruginosa (Rod shape)	Incubated for 24 hours under static conditions	PDMS (polydimethylsiloxane)	Pillar-like	3(μm)	D = 1.5 (μm)	4 (μm)	Mechanical properties of biofilm can be identified by the micropillar deflections which are caused by pressure [117]
Staphylococcus aureus (Spherical),	Incubated for 4 hours	poly(N-isopropylmethacrylamide) P(NIPMAM)	Pancake-like and circular	10-600 (nm)	–	–	The maximum bacterial adhesion reduction was found with thickest coating (h = 602 nm). [118]
Staphylococcus aureus (Spherical),	Incubated for 48 hours	titanium and tannic acid/gentamicin (TA/G)	Pillar-like	2 (μm)	D = 10 (nm)	2 (μm)	LbL coating of TA/G film showed 10-fold reduction of the number of attached bacteria on the surface with respect to bare titanium surface. [119]
Staphylococcus epidermidis and Staphylococcus aureus (Spherical)	2 or 5 days	Polyurethane-urea (PUU)	Pillar-like	690–700 (nm) 640-650 (nm)	410-430 (nm) 500- 560 (nm)	350-400 (nm) row separation 680- 750 (nm) diagonal separation 450-500 (nm) row separation 840- 900 (nm) diagonal separation	Pillars analysis exhibited replication accuracies of 99.8% and textured surfaces decreased the bacteria contact area by approximately 70%. [120]

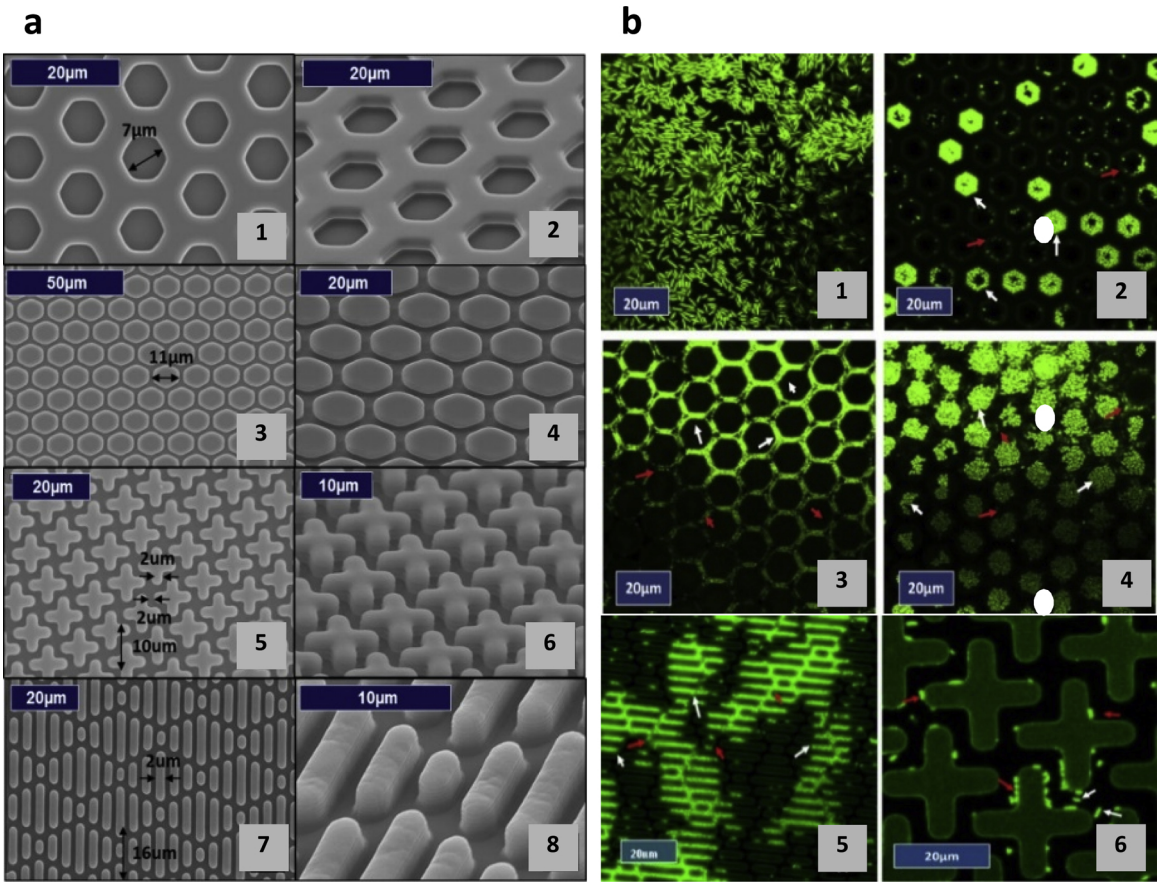

Fig. 2. Tailored surface topography with the aim of antibacterial activity. Top and perspective SEM images of the PDMS test patterned surface (1) and (2) HC-7-PDMS, (3) and (4) 11-H-PDMS, (5) and (6) C-5-PDMS and (7) and (8) Sharklet™ patterned surface. [106] b) Confocal images of *E. cloacae* growth on silicone elastomer after 48 h. (1) Smooth surface, the experimental control; (2) HC-7-PDMS, white arrow – pits with clusters; red arrow – isolated cells; (3) 11-H-PDMS, white arrow – depressed regions with clusters; red arrow–isolated cells; (4) 11-H-PDMS, white arrow – feature tops with cell clusters; red arrow – isolated cells; (5) Sharklet™ 2 µm spacing and 3 µm height, white arrow – bacterial clusters; red arrow – isolated cells and clusters in between ridges; (6) C-1-PDMS, white arrow – isolated cells; red arrow – isolated cells. "*Adapted with permission from R. Vasudevan, A. J. Kennedy, M. Merritt, F. H. Crocker, R. H. Baney, Colloids Surfaces B Biointerfaces 2014, Copyright (2019) Elsevier*" [106]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

3.2. Surface coating of nanoparticles

Surface coating is one of the most commonly used methods for the fabrication of antibacterial surfaces [36,63–66]. This method is based on the deposition of an antibacterial substance onto the substrate surface. The antibacterial effect stems out of one or multiple mechanisms as follows: (i) the coated surface is toxic for bacteria cells in contact, (ii) the coated substance releases an effective antibacterial agent, and (iii) the coating resists adhesion of bacteria [48]. This technique is mostly used in biomedical applications because, in this area, it is essential that surfaces remain antibacterial when applied in complex surroundings such as implanted in tissues [48,64,67]. One possible technique to overcome the temporary activity of antibacterial surfaces is to covalently anchor the antibacterial compounds to the substrate [66,68]. Different covalent anchored antibacterial agents such as, chitosan, quaternary ammonium compounds (QAC), and enzymes were recognized to disrupt bacterial cell membrane [66].

Silver-based coatings are generally used in medical devices because silver ions, which are released from a silver-coated surface, are able to kill both Gram-positive and Gram-negative bacteria [1]. Also, researchers have reported several coatings such as antibiotic-loaded, organic bactericide doped [69,70], inorganic bactericide doped [71,72], anti-adhesion coatings [73], and bioactive functionalized surface coatings [46,74], which can decrease the adhesion and growth of bacteria. The coating of inorganic NPs onto polymeric materials and the like is not straightforward largely due to the discrepancy in surface free energy between the two media [75]. This effect means that such coatings are not necessarily stable, especially against any requirement for washing procedures [75]. So far, most of the reported techniques for stable coating of inorganic nanostructured materials on surfaces employ a series of steps, including preparation, functionalization, final treatment, and curing [66,75,76]. These approaches are usually costly and time-consuming for high-volume industrial manufacturing production [77]. In addition, various shortcomings are evident during the use of such a surface coating technique [66,75]. One of the main disadvantages in this method is that bacterial cells can become resistant against antibiotics and antibacterial agents [1]. Another potential deficiency is that the concentration of the released antibacterial agents may not always sufficient to affect bacterial cells [78]. Also, the stability of the antibacterial agents on the target surface may not be adequate to retain long-term antibacterial behavior [40].

3.3. Layer-by-layer assemblies

The layer-by-layer (LbL) assembly technique was first reported by Decher et al. [12] in 1992 and involves the deposition of charged polyelectrolytes on an oppositely charged surface. There are two types of charged substrate surfaces: (i) naturally charged substrates, such as

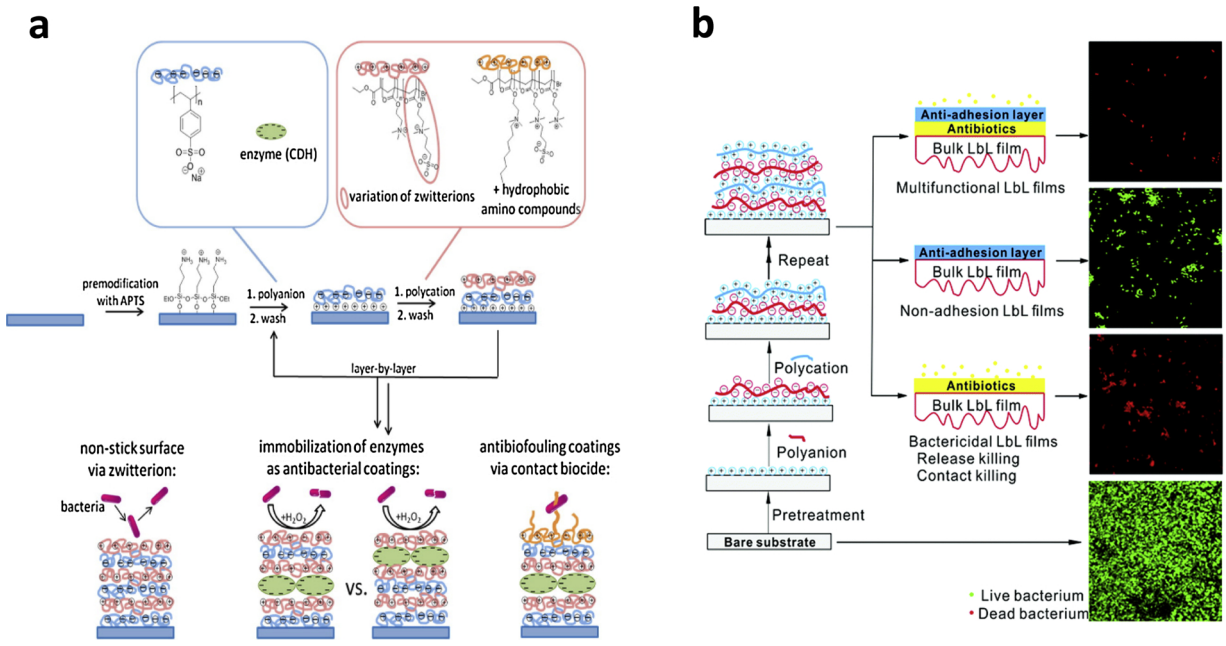

Fig. 3. Different types of antibacterial LbL films. a) Schematic representation of layer-by-layer assembly on APTS premodified silicon wafer or PDMS surfaces with different polymeric building blocks; polyanions consisting of poly(styrenesulfonate) (PSS) and cellobiose dehydrogenase (CDH) for antibacterial coating; polycations consisting of novel copolymers (PTMAEMA-co-PSPE) with varied sulfobetaine fractions for antifouling properties, and the optional addition of quaternary hydrophobic groups for contact biocide functionality. *"Adapted with permission from A. Vaterrodt, B. Thallinger, K. Daumann, D. Koch, G. M. Guebitz, M. Ulbricht, Langmuir 2016. Copyright (2019) American Chemical Society."* [107] b) Scheme of LbL assembly and the main antibacterial strategies. *"Adapted with permission from X. Zhu, X. Jun Loh, Biomater. Sci. 2015, Copyright (2019) Royal Society of Chemistry"* [79].

silicones, glasses and metals, and (ii) artificially charged substrates through techniques such as oxidation, silanization, and high energy electron irradiation [79].

In the LbL assembly process, the charged substrate surface is first soaked in a solution of polyelectrolyte with opposite charge. Subsequently, by rinsing the substrate surface with deionized water, the loosely-adsorbed polyelectrolyte chains are removed from the surface and only the ones with strong electrostatic interaction with the surface remain. The surface is then coated with another layer of polyelectrolyte with a charge opposite to that of the first coating using a similar costing process. This procedure is repeated to coating more layers of polyelectrolyte with alternating charge [80]. By adjusting the number of deposition cycles, desired thicknesses and structures of the LbL-assembled films can be fabricated on the surface. The functionality of LbL films will be determined based on the characteristics of the deposited components [79]. The existing antibacterial LbL films can be categorized into three groups based on their antibacterial mechanisms: bactericidal, non-adhesive and multifunctional films (Fig. 3). The critical step of the LbL assembly technique is the design and synthesis of the charged functional polyelectrolytes. Many types of charged polyelectrolyte with different functional materials, such as metal ions NPs, biological macromolecules, organic molecules, and viruses can be used to form the LbL films because the dominant force in LbL approach is electrostatic interaction. Consequently, a wide range of substrates, coating materials, and assembly methods can be used in the LbL assembly technology [81–83]. Specifically, LBL assembly lately emerged as a suitable fabrication technique for incorporation of one or several antibacterial biocompatible functional components including NPs into materials [84–87]. Antibacterial surfaces/films biocompatibility plays an important role in several applications such as limiting the infections in wounds and the burn therefore, developing protective dressings to stop bacteria growth without any side effects are vital [88]. Researchers utilized the LBL method to develop biocompatible antibacterial surfaces due to the versatility of coating materials in this fabrication technique. Recently, Francesko et al. presented a biocompatible antibacterial nanobiocomposite which not only limits the growth of Gram-negative (*E.coli*) and Gram-positive(*S. aureus*) bacteria, but it also exhibits a low level of toxicity to human skin cell lines (fibroblasts and keratinocytes) [89]. The antibacterial nanocomposite was achieved through the consecutive deposition of silver NPs and hyaluronic acid (HA) on a silicon surface.

4. Antibacterial activity and nanotoxicology of nanoparticles

4.1. Mechanism of nanoparticle's antibacterial activity

The precise and complete mechanisms involved with regard to NP toxicity against bacteria cells still remain to be elucidated [90]. NPs are able to bond to the bacteria by electrostatic interaction and disrupt the integrity of the bacterial outer membrane [29]. Generally, nanotoxicity is conferred through the excitation of oxidative stress (reactive oxygen species), following the introduction of NPs [33]. Particular emphasize and focus of previous studies was given to the generation of reactive oxygen species (ROS) which includes peroxide, hydroxyl radicals, and hydrogen peroxide. ROS has been revealed as one of the key features for several NPs antibacterial mechanisms such as damage to the cell wall, membrane permeability variation, and penetration of NPs ion because of changes in proton motive force [90–92]. Additionally, ROS can decrease the activity of certain periplasmic enzymes and disrupt proteins which are vital to sustaining normal physiological developments in bacterial cells [93]. According to previous studies, several processes can be named which induce the antibacterial activity of NPs Alongside with ROS generation such as, i) disturbance for cell membrane; ii) penetration through the cell membrane; and iii) induction of intracellular interactions with mitochondria and DNA (Fig. 4a) [94]. Several researchers have demonstrated that Gram-positive bacteria are extra resilient to NP mechanisms of action [95,96]. Tables 3 and 4 show a summary of recent studies on the antibacterial properties and their mechanisms of several metallic and metal oxide NPs against Gram-positive and Gram-negative bacteria [33].

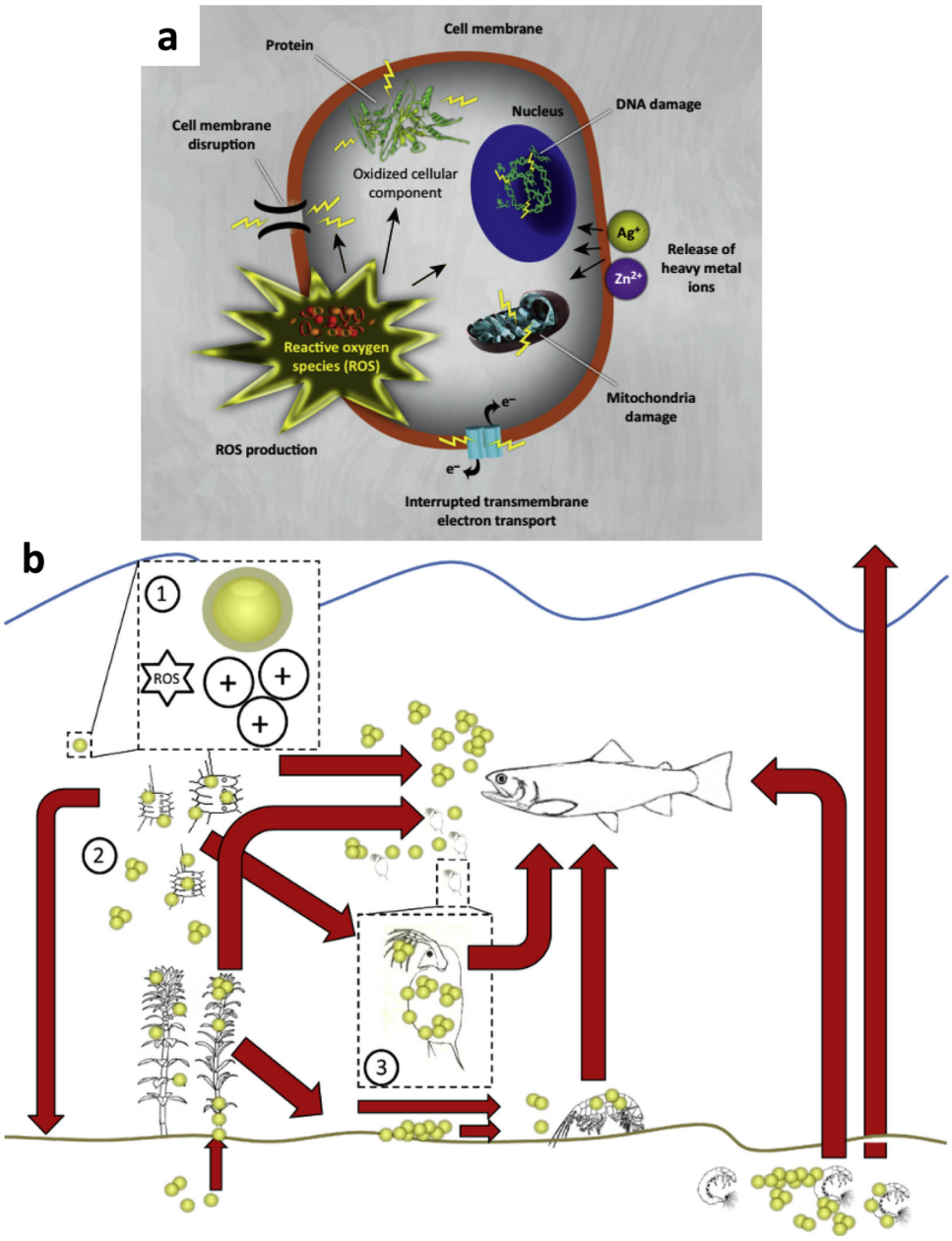

Fig. 4. a) Mechanisms of toxicity of nanoparticles (NPs) against bacteria. NPs. NPs ions (e.g., silver and zinc ions) can produce free radicals, resulting in induction of oxidative stress (i.e., reactive oxygen species; ROS). The produced ROS can irreversibly damage bacteria (e.g., their membrane, DNA, and mitochondria), resulting in bacterial death. "*Adapted with permission from M. J. Hajipour, K. M. Fromm, A. Akbar Ashkarran, D. Jimenez de Aberasturi, I. R. de Larramendi, T. Rojo, V. Serpooshan, W. J. Parak, M. Mahmoudi, Trends Biotechnol. 2012. Copyright (2019) Elsevier*" [33]. b) Effects of metal NPs leakage of metal NPs in into water environment. Red arrows show potential pathway of nanoparticles toxicity in aquatic environments considering the (1) toxic properties, (2) biomagnification potential induced by adsorption leading to integration, (3) adsorption of engineered nanoparticles onto aquatic organisms. *"Adapted with permission from M. Bundschuh, F. Seitz, R. R. Rosenfeldt, R. Schulz, Freshw. Biol. 2016, Copyright (2019) John Wiley and Sons"* [99]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

4.2. Toxicity of nanoparticles to beneficial bacteria in the environment

In contrast to the significant amount of research conducted on the antibacterial activity, only a handful of studies have reported on the *in vivo* toxicity of metal oxide NPs against mammalian cells and higher-order cells [97,98]. Furthermore, the absence of a standard method is one of the major deficiency of the current studies on the nanotoxicity of NPs. Specifically, different cell lines, exposure time to NPs, and different physicochemical characteristics of NPs cause difficulty to analyze toxicity activity of NPs.

The use of metal NPs in medical science and commercial products referred to above leads to leakage of such into the environment (e.g., soil and water) and in turn to the death of several beneficial microorganisms (Fig. 4b) [33]. Therefore, it is becoming increasingly apparent that environmental protection from NPs should be further investigated [99]. Indeed, it is considered that one of the most serious threats to useful bacteria (e.g. bacterial communities in ecosystems) is the spread of metal NPs into the environment [100]. Many bacteria are beneficial for the ecosystem and the environment because they are crucial in element cycling, bioremediation and nitrogen fixation for plants. This is especially the case in the nitrification procedure, whereby ammonium nitrogen is transformed to nitrite by ammonia-oxidizing bacteria, and hence to nitrate by nitrite-oxidizing bacteria. The nitrifying bacteria are effective in the places that have a high amount of ammonia. However, silver metal NPs (Ag NPs, size: < 5 nm) are toxic to nitrifying bacteria, because the bacterial outer membrane, which contains ammonia-oxidation enzymes, interacts with silver NPs. [33]. Accordingly, the elimination of beneficial bacteria from the environment leads to reduced nitrogen removal and inhibits plant growth. Under these circumstances, researchers should consider the impacts of the metal NPs on human health and the environment, in spite of their useful features.

4.3. Examples of toxicity of nanoparticles to mammalian cells

Introduction of NPs into the environment may also cause deleterious effects on mammalian cells, especially considering their relative surface area increment which means nanometer-sized particles are highly

Table 3
Different nanostructured materials and their toxic effects in Gram-Negative bacteria.

Bacteria	Material Synthesis	Material Characterization	Utilized dosage	Toxicity Mechanism	Consideration	Refs
K. pneumoniae	Au NPs	10 nm and 15 nm measured by AFM	1 mM gold chloride	NPS attach to the cell surface and this interaction causes structural changes and damage and disturbs cell functions	Nanosized AuNPs and narrow size distribution offer advantages for self-assembled monolayer formation.	[121]
	Ag Caron complex L-tyrosine polyphosphate NP (SCC23-LTP NPs)	~800 nm (size defined by DLS)	(MBC) NA (MIC) > 10 mg/l	–	–	[122]
	Ag NPs	43 nm (Hydrodynamic size in XRD) Surface area: 26 m2/g	30 mg/l	Electrostatic interaction, adsorption, and penetration of NPs and toxicity	The adsorption of Ag NPs increases at 20 8C compared to 37 8C	[123]
	NO NPs	10–15 nm (size defined by TEM)	(MIC) 10 mg/ml in 24 h	Alteration of the bacterial membrane, antimicrobial effects via nitrosation of protein thiols and the nitrosylation of metal centers	NO oxidized to RNS, which exert antimicrobial effects	[124]
P. aeruginosa	Fe_2O_3 NPs	2-540 nm	10 μg/mL	deregulating host innate immunity	harmful to human health	[125]
	NO NPs	8–15 nm (size defined by TEM)	(MIC) 10 mg/ml in 16h	Alteration of the bacterial membrane, antimicrobial effects via nitrosation of protein thiols and the nitrosylation of metal centers	NO oxidizes to RNS which exert antimicrobial effects	[124]
	NO-releasing MAP3 (N-methyl amino propyltrimethoxysilane) Si NPs	80–100 nm (size defined by AFM)	8 mg/ml	Biofilm killing due to electrostatic properties of NO-releasing NPs and increased NO delivery to biofilm-based microbes	Rapid delivery of NO may be more effective at biofilm killing than slow NO delivery	[126]
	TiO_2	10–25 nm (ST-01, Ishihara Sangyo Kaisha Ltd., Osaka, Japan	10 mg/l	Photoactivation of TiO2 promotes bactericidal effect Peroxidation of the polyunsaturated phospholipid of the membrane, loss of respiratory activity	–	[39]
	Ag NPs	~ 6 nm measured by TEM	0.316 μg/mL	–	low cost and efficient method of fabricating Ti/TiO2 surface with Ag NPs	[127]
		300-800 nm	1 mM	Ag NPs anchor to the bacterial cell wall and penetrate it	Applicable to use as an alternative antibacterial to reduce the burden of multidrug resistance.	[128]
		1–10 nm measured by TEM	25–100 mg/l	Disturbs permeability, respiration, and cell division, interacts with the cell membrane and sulfur- and phosphorus-containing compounds	–	[23]
		390 and 410 nm measured by Malvern Zetasizer Nano ZS (Malvern Instruments Ltd, Malvern, UK)	0.862 mg/mL	damage in cell membranes leading to structural changes, cause bacteria more permeable	Efficient antibacterial ability *in vitro* and *in vivo* could be used as an alternative to conventional antibiotic therapy.	[129]
	ZnO	10–20 nm (size defined by TEM)	1–4.25 mM in 100 L of LB	Bacterial attachment by Electrostatic interaction, ROS generation, membrane disruption, and disturbance of permeability	–	[130]

(*continued on next page*)

Table 3 (*continued*)

Bacteria	Material Synthesis		Material Characterization	Utilized dosage	Toxicity Mechanism	Consideration	Refs
E. coli	Au NPs		10 nm and 15 nm measured by AFM	1 mM gold chloride	NPS attach to the cell surface and this interaction causes structural changes and damage and disturbs cell functions	Nanosized AuNPs and narrow size distribution offer advantages for self-assembled monolayer formation.	[121]
	Extracellular biogenic synthetic Ag NPs by Trichoderma viride fungi		5–40 nm (size defined by TEM)	(MIC) 30 μg/ml	Ag NP–ampicillin leads to cell wall lysis, penetration of Ag NPs, and prevents DNA unwinding	Biogenic Ag NPs have synergistic effects with antibiotics	[131]
	Ag-doped bioactive glass nanoparticles	95.61SiO2-4.26CaO-0.12Ag2O	365 nm	1 mg/mL	–	The modified BGNs remain monodisperse, bioactive, and acquire antibacterial capability	[132]
		95.46SiO2-4.35CaO-0.19Ag2O	373 nm				
		95.69SiO2-4.07CaO-0.24Ag2O	367 nm				
	NO-releasing MAP3 (N-methyl amino propyltrimethoxysilane) Si NPs		80–100 nm (size defined by AFM)	8 mg/ml	Biofilm killing due to electrostatic properties of NO-releasing NPs and increased NO delivery to biofilm-based microbes	Rapid delivery of NO may be more effective at biofilm killing than slow NO delivery	[126]
	Al_2O_3 NPs		50–70 nm (Zhejiang Hongsheng Material Technology Co.) +30 mV	20 mg/l	Bacterial attachment (electrostatic interaction) Damage to the bacterial cell wall and increased permeability	Toxicity of NPs is from their high tendency to bind to the cell walls	[133]
	ZnO NPs		~20 nm (Zhejiang Hongsheng Material Technology Co.) –5 mV	20 mg/l	–	Toxicity of NPs is from their high tendency to bind to the cell walls	[113,133,134]
	TiO_2 NPs		~50 nm (Zhejiang Hongsheng Material Technology Co.) –21 mV	20 mg/l	No toxicity in dark condition		
	SiN-PMAA		D ≈ 100 nm L ≈ 40 μm	NA	Interactions of SiN-PMAA surfaces with bacterial cells changes in the environmental pH.	Switchable capability for killing and releasing bacteria.	
	NiO NPs		~20–30 nm (NanoAmor, Houston, USA)	20 mg/l	Growth inhibition (in aqueous medium). Significant damaged cellular functions, physical/mechanical stresses on cellular structure integrity (in aerosol exposure)	A synergistic effect between the soluble ion stress and the nano-related stress (in aerosol exposure of NiO, ZnO, CuO)	
	Nano PP with TiO2 NPs and clay	nPP/Clay	200 nm measured by the image processing method	–	–	An effective method of entrapment of nanoparticles in wet filtration	[135]
		nPP/TiO_2 NP	250 nm measured by the image processing method				
	zero valent Cu NPs (ZVCN)		~25 nm (Sun Innovations, USA)	–	The release of Cu ions and generation of hydroxyl radical in the cytoplasm	–	[136]
	TiO_2 NPs		20 nm ST-01 (Ishihara Sangyo Kaisha Ltd.)	10 mg/l	Photoactivation of TiO_2 promotes the bactericidal effect. Peroxidation of the polyunsaturated phospholipid of the membrane, loss of respiratory activity	–	[39]
	Ag NPs		1–10 nm (size defined by TEM)	25–100 mg/l	Disturbed permeability, respiration, and cell division Interacts with the cell membrane and sulfur- and phosphorus-containing compounds	–	[137]
	Ag NPs		9-27 nm measured by TEM	80 μg/mL	NP attached to the surface of the bacterial cell membrane and consequently, permeability and respiration, are disturbed	it can be used as an effective growth inhibitor against various pathogenic bacterial strains in various medical device	[138]
	ZnO		25–40 nm (core size in TEM)	8 and 80 ng/ml	ZnO: cellular uptake, ROS generation and has no significant toxicity. A frameshift mutation in the presence of metabolic activation system (S9).	–	[139]

(*continued on next page*)

Table 3 (*continued*)

Bacteria	Material Synthesis	Material Characterization	Utilized dosage	Toxicity Mechanism	Consideration	Refs
Sal. typhimurium	TiO2	40–60 nm (core size in TEM)	8 and 80 mg/ml	TiO2: cellular uptake, ROS generation and has no significant toxicity. Frameshift mutation independent of metabolic activation system(s9)	Sh. oneidensis MR-1 tolerate against NPs due to production of a large amount of EPS and reduction of ionic Cu	[139]
	ZnO	25–40 nm (core size in TEM)	8 and 80 ng/ml	ZnO: cellular uptake, ROS generation and has no significant toxicity. Frameshift mutation in the presence of metabolic activation system (S9).	–	
Sh. oneidensis MR-1	Cu-doped TiO_2	20 nm measured by TEM	20 mg/L	–	S. oneidensis MR-1 displayed an excellent resistance to metal NPs.	[140]
P. putida KT2442	CuO	25–40 nm Sigma–Aldrich	10 mg/l	Cell membrane damage and bactericidal effect	Nano-Ag and nano-CuO NPs have different targets for killing bacteria	[100]
	Ag	10 nm Sigma–Aldrich, St. Louis, MO, USA	1 mg/l			
	ZnO	50–70 nm Sigma–Aldrich	10 mg/l	Bacteriostatic effect	–	[100]
		< 100 nm	1 mg/mL	ROS release might probably be the most influencing antibacterial factor.	promising properties in biofilm prevention in flowing systems, including membrane separation,	[38]
C. metallidurans CH34	TiO_2	< 25 nm (size defined by TEM	–	C. metallidurans CH34 is resistant to NPs. TiO_2 and Al_2O_3 can internalize in this bacterium but these NPs do not cause death	The resistance of C. metallidurans CH34 may be related to overexpression of protective components or by efflux systems	[141]
	Al_2O_3	< 25 nm (size defined by TEM)	–			
	Multiwalled-carbon nanotubes (MWCNTs)	< 25 nm (size defined by TEM)	–	C. metallidurans CH34 is resistant to NPs. The MWCNTs cannot internalize in this bacterium		

reactive species [101]. The presence of these particles can result from industrial processes where a broad range of parameters, such as production volume, industrial applications, and manufacturing settings can affect the diffusion rate of harmful elements in the environment. While there have been a few studies on the toxicity of NPs to mammalian cells, it is clear that much further research is required to elucidate mechanisms of the nanotoxicity of the NPs [101]. In this regard, we summarize the role played by three NPs which have been employed widely in industry.

The first particle to be discussed is those composed of silver. This metal has been used in medicine to treat infections since medieval times. At the present time, silver NPs are extensively commercialized as an antibacterial/antimicrobial agent in a broad range of products [101]. It has been shown that these NPs possess a great ability to kill bacteria[63] but that they are also toxic to mammalian cells [102]. It is notable that the toxicity of silver NPs depends on their size and shape; particles with a diameter of less than 10 nm can readily penetrate the cell membrane. A study on the light-producing bacteria showed that silver NPs can breach the cell wall and cause cell deformation [103]. Also, several studies have claimed that silver NPs can damage DNAs and prevent their ability to replicate in different cells. Silver NPs are toxic to mammalian cells, such as rat liver cells (as a model for human toxicity after inhalation), neuroendocrine cell lines (as a specimen which is similar to human brain cells) [104]. With respect to the harmful impact of silver NPs on mammalian cells, it has been shown that these particles can significantly damage the male reproductive system [81–83]. There is also proof that silver NPs can be harmful when used and introduced via implanted medical devices [102].

Titanium dioxide (TiO_2) NPs are used in large amounts - about 1000 kg per company in one year [102]. Hence, the toxicity of TiO_2 NPs has an important role in human health and risk management. Although microscale materials are normally considered to be harmless, recent studies have indicated that persistent inhalation of TiO_2 NPs is dangerous. In vitro experiments have confirmed that TiO_2 NPs can interrupt immune cell function [102]. Additionally, it has been demonstrated that inhalation of TiO_2 NPs causes lung damage in mice such as pulmonary fibrosis, inflammation, and instigation of lung tumors [101,102].

Zinc oxide NPs are commonly used in cosmetics, such as sunscreens, toothpaste, and beauty products [101]. These NPs can directly affect human health. Previous studies have exhibited that ZnO NPs can be toxic to mammalian cells, even at low concentrations [41]. An experiment conducted on mice demonstrated that various conditions can result, ranging from kidney failure and liver damage to death. Another study reported injuries of different mice organs by ZnO NPs, such as the spleen, heart, pancreas, and liver [38]. Recently, it has been shown that zinc oxide NPs causes genetic damage when applied onto the skin [105].

5. Final remarks

There is no doubt that various aspects of nanotechnology have become an important factor in our daily lives through the provision of a plethora of applications ranging from medicine to industrial processing. One such area of this technology which has seen considerable success is the extensive use of NPs as antibacterial materials. Antibacterial capability of metal NPs depends on two parameters: the physical and chemical properties of specific particles and secondly the particular type of bacteria involved in terms of toxicity. Unsurprisingly, it is the case that there is no generalized theory that can be applied to such antimicrobial activity since it would be expected that different bacteria will respond to particles in a variety of ways. Accordingly, it will be necessary to explore such antibacterial effects through careful studies on targeted bacteria.

Finally, it is becoming increasingly apparent that the influence of nanotechnology, and in particular NPs, on the environment and the

Table 4
Different nanostructured materials and their toxic effects in Gram-Positive bacteria.

Bacteria	Material Synthesis	Material Characterization	Utilized dosage	Toxicity Mechanism	Consideration	Refs
S. epidermidis	Silver NP- anchored to an amino-silanized glass surface	Ag nanoparticles with size < 50 nm measured by TEM	0.73 μg/cm^2	Ag^+ ions interact with sulfur- or phosphorus-containing groups belonging to proteins of the bacterial cell wall or plasma membrane, create membrane holes	excellent stability in an aqueous medium and prolonged release and high local concentration of Agþ without any detaching of AgNPs	[126,142,143]
	zwitterionic block copolymer micelles (BCMs)	~20 nm measured by TEM	2.5 mg/mL	The anti-adhesive property was provided by the zwitterionic coronae of the BCM and releasing antibacterial agents from the surface.	the number of layers deposited at the surface affected the anti-adhesive property and 3-layer films were the most anti-adhesive coating against S. aureus	
	NO-releasing MAP3(N-methyl amino propyltrimethoxysilane) Si NPs	80–100 nm measured by TEM	8 mg/mL	Biofilm killing due to electrostatic properties of NO-releasing NPs and increase NO delivery to biofilm-based microbes	Rapid delivery of NO may be more effective at biofilm killing than slow NO delivery	
S. aureus	Ag NP	5-100 nm measured by TEM	80 to > 200 mg/mL	Electrostatic attraction between negatively charged AgNPs and positively charged residues of the integral membrane proteins on the bacterial surface	All AgNPs were found to be highly toxic to the bacterial strains and their antibacterial efficacy increased with lowering particle size	[144]
	Ag–ZnO nanocomposites	Ag nanoparticles 53.07 nm and Zinc oxide 10.9 nm measured by TEM	2 μg/mL	binding and internalization of Ag–ZnO nanocomposites.	Certain polymeric matrices can be modified by introducing Ag–ZnO nanocomposites as a new approach to preservation	[145]
	Carboxyl-grafted SPIONs	10–20 nm measured by TEM	0.35 mg/mL	An external magnetic field could target carboxyl-grafted SPIONs into a biofilm and increase antibacterial efficacy	Carboxyl-grafted SPION, APTESgrafted and bare SPION Internalized into the cell but does not affect mammalian cell adhesion and spreading	[146]
	APTES-grafted SPIONs	10–20 nm measured by TEM	0.35 mg/mL	ROS generation, electrostatic interaction between NPs and bacteria		
	Bare SPIONs	10–20 nm measured by TEM	0.35 μg/mL			
	PEGylated SPIONs	10–20 nm measured by TEM	0.35 μg/mL	No bacterial toxicity	PEGylated SPION does not internalize into the cell	
	Ag-coated SPIONs	15–20 nm measured by TEM	80 μg/mL	Bacterial toxicity by penetration within the biofilm and increase of the bacterial toxicity in the presence of external magnetic field, ROS generation, electrostatic interaction, and physical damage of bacteria	Ag-coated SPION and Ag–Au-coated SPION are fully compatible with the cell	[147]
	Ag–Au-coated SPIONs	20–30 nm measured by TEM	80 μg/mL			
	Au-coated SPIONs	25–40 nm measured by TEM	80 μg/mL	Spion-Au NPs have slight antibacterial activity only in the presence of external magnetic field due to penetration within biofilm of bacteria	–	
(Halophilic) bacterium sp. EMB4	ZnO	< 100 nm Measured by TEM	2 or 5 mM	Electrostatic interaction, morphological changes in the presence of bulk and nano ZnO, increase in membrane permeability and ZnO accumulation in the cytoplasm	–	[148]
	Ag	< 100 nm measured by TEM	2 or 5 mM	Bulk Ag and nanosized Ag did not affect the growth and cell wall	–	
Vancomycinresistant Enterococcus	Ag Caron Complex-L-tyrosine polyphosphate NP(SCC23-LTP NPs)	700–800 nm (size defined by DLS)	(MBC) NA (MIC) 10 mg/L	–	–	[122]
	vancomycin NPs	350 nm in DCM/ EtOH and 250 nm in DMF	0.8 μg/mL	Acting on the external wall of the bacteria by inhibiting proper cell wall synthesis	In vivo evaluation of this biomaterial is in progress	[149]

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Table 4 (*continued*)

Bacteria	Material Synthesis	Material Characterization	Utilized dosage	Toxicity Mechanism	Consideration	Refs
B. subtilis	ZnO NP	34.22 nm measured by TEM	10 mg/mL	inhibiting	The bactericidal effect is independent of Ag concentration	[150]
	Ag doped ZnO NPs $Ag_{0.1}ZnO_{0.9}$	47.85 nm measured by TEM	4 mg/mL	the enzymatic system of the respiratory chain by altering		
	$Ag_{0.1}ZnO_{0.9}$	24.41 nm measured by TEM	8 mg/mL	the DNA synthesis also, silver nanoparticles enter through the cell		
	$Ag_{0.1}ZnO_{0.9}$	23.50 nm measured by TEM	8 mg/mL	membrane, causing massive cell damage		
	$Ag_{0.1}ZnO_{0.9}$	59.07 nm measured by TEM	6 mg/mL			
	Ag NP	9-27 nm measured by TEM	50 μg/mL	NP attached to the surface of the bacterial cell membrane and consequently, permeability and respiration, are disturbed	it can be used as an effective growth inhibitor against various pathogenic bacterial strains in various medical device	[138]
	ZnO NP	< 100 nm (Cat. No. 544906, Sigma–Aldrich)	10 mM	Bulk and nanosized forms of ZnO and Ag have a marginal reduction in the specific growth rate and viable count	Toxicity towards Gram-positive cells is significantly less, because of the presence of thicker PG layer	[138]
	Ag NP	< 100 nm (Cat. No. 576832, Sigma–Aldrich)	10 mM			
	Ag NP	2–4 nm (size defined by TEM)	ND	The release of Ag1 + and Cu2 +, electrostatic interaction, cell wall damage, rupture of the plasma membrane, and disrupt the biochemical process	There are more amines and carboxyl groups on the cell surface of *B. subtilis* and therefore bind to NPs	[138]
	CuO NP	8–10 nm (size defined by TEM)	ND			
	$Al2O_3$ NP	40–70 nm (purchased from Zhejiang Hongsheng Material Technology Co., China) ZP: +30 mv	20 mg/L	bacterial attachment (electrostatic interaction) Damage to the bacterial cell wall and increase the permeability	Toxicity of NPs is from their higher tendency to attach to the cell walls	[138]
	TiO_2	40–60 nm (purchased from Zhejiang Hongsheng Material Technology Co) ZP: –21 mv	20 mg/L	TiO2 has no toxicity in dark condition		
M. smegmatis	Cu-doped TiO2 NPs	~20 nm measured by TEM	20 mg/L	The release of Cu2 +, decreased enzymatic activity NADPH production, no cell damage, no internalization of NPs	In the presence of EDTA, the antibacterial activity of Cu-doped TiO2 decreases significantly	[140]
	Au NPs	1.6–2.7 nm measured by TEM	1 to 16 μM	inhibition depends on the specific combination of ligands attached to the NP surface	This formulation reveals harmful effects on red blood cells	[151]
B. cereus	Au NPs	10 nm and 15 nm measured by AFM	1 mM gold chloride	NPS attach to the cell surface and this interaction causes structural changes and damage and disturbs cell functions	Nanosized AuNPs and narrow size distribution offer advantages for self-assembled monolayer formation.	[121]

human condition requires much further examination in the future. It will be mandatory in the coming years with respect to newly-designed antibacterial surfaces through metal NP technology that their effects on the environment, human and other organisms in terms of their toxicity must be taken into account.

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