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Antibacterial activity of nanoparticles and nanomaterials: a possible weapon in the fight against healthcare-associated infections

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Abstract. – Healthcare-associated infections are a serious threat in terms of morbidity and mortality for all patients receiving healthcare. The problem is aggravated by the increasingly widespread phenomenon of antibiotic resistance, with some microorganisms now resistant to all or almost all the currently available antibiotics. Nanomaterials are compounds used by many different industrial fields and they are currently studied for their intrinsic antimicrobial properties. To date, many researchers have considered using many different nanoparticles and nanomaterials to produce surfaces and medical devices with intrinsic antimicrobial features. Many compounds have shown very interesting and effective antimicrobial capacities and could be used, in the future, to manufacture new hospital surfaces and medical devices. However, many studies have to be carried out to evaluate the effective potential use of these compounds. The aim of this paper is to review the main literature regarding this topic, focusing on the main types of nanoparticles and nanomaterials studied for this purpose.

Key Words:
HAIs, Nanoparticles, Antimicrobial activity.

Introduction

Healthcare-associated infections (HAIs) are currently one of the most demanding challenges of public health worldwide. It is estimated that in Europe, 6.5% of patients admitted to an acute care hospital develop an HAI[1]. In addition, there is a growing concern in the scientific community regarding the increasingly widespread and consistent phenomenon of antibiotic resistance. Various microorganisms are able to develop resistance towards antibiotics with different mechanisms of action (inhibition of cell wall synthesis, DNA replication and protein synthesis)[2]. Indeed, microorganisms have gradually developed various resistance mechanisms against almost all of the available antibiotics[3]. Specifically, we refer to the so-called 'ESCAPE' microorganisms - a term introduced by the Centers for Disease Control and Prevention (CDC) - which are *Enterococcus faecium, Staphylococcus aureus, Clostridium difficile, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacteriaceae*[4,5]. These multidrug-resistant (MDR) or, in some cases, pan-resistant pathogens are the world's leading cause of HAIs[6-9]. These bacteria are widely spread in hospital environments and surfaces on which they are able to survive for a long period of time and, therefore, cross-contaminate medical devices, with a high risk of passing to patients[10-12].

Bacterial resistance mechanisms can be classified as naturally intrinsic (the microorganism is naturally resistant, for example, due to the lack of pharmacological target), induced (i.e., resistance genes are expressed after exposure to the drug) or acquired (*via* horizontal gene transfer or mutations)[3]. There are four main types of mechanisms involved in antibiotic resistance. The first is based on a decrease in intracellular drug accumulation and can occur 1) through reduced membrane permeability or 2) through active extrusion of the drug *via* efflux pumps. The second mechanism is enzymatic inactivation or modification of the drug chemical structure. The third mechanism is modification of the pharmaceutical target. Finally, there is the alteration of some metabolic pathways[13-15]. The CDC reported[16] that in 2019 in the USA, 2.8 million people were infected with antibiotic-resistant bacteria or fungi, and more than

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35,000 people died as a result. Therefore, the scientific community has directed an immense amount of effort to study different materials with antimicrobial properties. In this view, nanotechnologies and the synthesis of various nanosized molecules potentially applicable as antimicrobial agents have received great attention[17]. Nanoparticles (NPs) could be used as a coating for hospital surfaces and for manufacturing medical devices as well as a mean to deliver molecules with antimicrobial activity, to produce a synergistic effect[18].

Nanoparticles and Nanomaterials

NPs are defined by the International Organization for Standardization (ISO)[19] as nano-objects that are entirely nano-sized. NPs can be of different shapes (spherical, cylindrical and conical), dimensions (as long as they remain between 1 and 100 nm in diameter) and can be composed of one or more layers[20]. On the other hand, nanomaterials refer to materials in which at least one of their dimensions is less than 100 nm[21]. As shown in Figure 1, Joudeh and Linke[19] classified nanomaterials based on how many dimensions are on nanoscale:

- zero dimensional nanomaterials, in which all three dimensions are nanoscale (fullerenes and quantum dots);
- one-dimensional nanomaterials, in which one dimension is greater than 100 nm (nanotubes, nanofibers);
- two-dimensional nanomaterials, in which two dimensions are greater than 100 nm (nanosheets, nanofilms, and nanolayers);
- three-dimensional nanomaterials, in which all three dimensions are greater than 100 nm due to secondary cluster of NPs (loose powders, NP dispersions, arrays of nanowires and nanotubes, etc.).

Synthesis of Nanoparticles

NPs have been studied for a long time to find correlations between their features (size, shape, height, surface and improved permeability) and antimicrobial properties in order to optimize their synthesis for use in the biomedical field. Multiple techniques have been used to fabricate NPs and nanomaterials; they are categorized into a bottom-up or top-down method[20]. The bottom-up method, also called the constructive method, starts from the atom up to the synthesis of NPs [the sol-gel process, spinning, chemical vapor deposition (CVD) and biosynthesis]. The top-down or destructive method is based on reducing a bulk material to NPs through mechanical milling, nanolithography, laser ablation, sputtering and thermal decomposition. Green synthesis of metal-based nanomaterials has also been discussed in recent years[22]. This approach uses bioactive agents such as plant materials, microorganisms and various organic waste as a starting point. All of this is done to significantly reduce the risk of environmental pollution.

Mechanisms of Toxicity

To be considered an excellent antimicrobial agent, NPs must have the ability to bind to microorganisms and slow or inhibit their growth. This binding occurs *via* a strongly positive zeta potential that promotes the interaction of NPs with cell membranes. This interaction can lead to the rupture of the cell membrane and a reduction in their vitality or to a greater penetration of the NPs inside the bacterial cell[17]. Obviously, the antibacterial action of NPs is also influenced by their nature, their size, form and charge[23,24]. In any case, several models have been proposed to explain the antibacterial action of these NPs.

Mechanical Membrane Damage

Membrane damage or rupture is a non-specific mode of action. The existence of this effect has been suggested by studies[25] in which bacterial cells, following treatment with NPs, showed abnormal membrane permeability, leading to death. Gram-negative bacteria are more sensitive to this action due to their thinner membrane (3-4 nm) compared with gram-positive bacteria, which have a thick layer of peptidoglycan and thus a much thicker membrane (30 nm)[26].

Release of Harmful Ions

Several NPs can release ions that can interfere with the functionality of bacterial proteins. For example, silver nanoparticles (AgNPs) release Ag ions that inhibit respiratory enzymes and DNA replication and compromise membrane permeability[27,28].

Reactive Oxygen Species Generation

When NPs come into contact with the microbial cell membrane, they can also trigger a series of oxidative processes that will lead to the production of reactive oxygen species (ROS). These compounds can damage cell constituents, alter

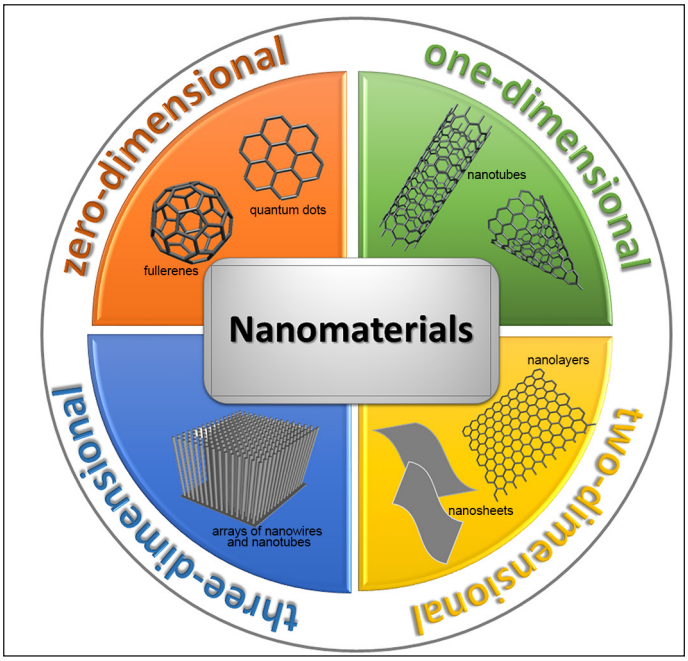

Figure 1. Classification of nanomaterials based on how many dimensions are on nanoscale.

membrane integrity and permeability, generate protein radicals[29], promote lipid peroxidation[30] and DNA strand breaks and modify nucleic acids[31]. In addition, gene expression can be modulated *via* activation of redox-sensitive transcription factors[32], and inflammation can occur through signal transduction[33].

Alteration of Protein Expression

NPs directly affect and create various alterations in bacterial metabolism. Indeed, researchers[34,35] have shown, through proteomics, that some NPs, such as magnesium oxide nanoparticles (MgONPs) or copper oxide nanoparticles (CuONPs), can alter the expression of specific proteins, which results in a reduction in cellular metabolic activity. Other species such as titanium dioxide nanoparticles (TiO_2NPs) affect the synthesis of adhesion proteins, which are required for biofilm formation[36].

Classification of Nanoparticles

NPs are classified according to their constituents into three categories: inorganic, carbon-based and organic[20]. The different types of NPs studied for their antimicrobial activities are summarized in Table I.

Inorganic Nanoparticles

Inorganic NPs include metal, ceramic and semiconductor NPs. Metallic NPs are made entirely of metal precursors and are typically classified as metal-based or metal oxide-based.

Metal-Based Nanoparticles

Metal-based NPs are composed of metals and synthesized with both destructive and constructive methods. Metal-based NPs can be synthesized from almost any metal[37], but copper (Cu), gold (Au), iron (Fe) and Ag are most often used. These nanoparticles have different properties (size, shape, color, structure, density, ratio between surface area and volume, surface charges, and reactivity).

Gold nanoparticles

Gold nanoparticles (AuNPs) have a diameter between 1 and 100 nm. If these particles are dispersed in an aqueous matrix, it is called colloidal gold. These NPs have aroused great interest because of their low toxicity. Moreover, they are easily manufactured and have a highly specific target[38]. AuNPs have shown[39,40] great versatility: they have potential use in different settings such as water hygiene management and can present anti-HIV activity when functionalized. They are often used for their antibacterial properties, despite having weak antimicrobial efficacy against

both gram-negative and gram-positive bacteria compared with other metal-based NPs. However, they are considered an excellent candidate for antibiotic complement. The antimicrobial effect is greater if AuNPs are functionalized due to their ability to behave like darts, generating holes in the bacterial cell wall and membrane. Such damage to the cell wall kills the microorganism due to the loss of cell content[41]. Furthermore, some studies[42] have shown the ability of AuNPs to bind bacterial DNA, preventing its unwinding. This leads to transcription and therefore protein synthesis blockade. These antimicrobial effects have also been shown[25] against MDR pathogens. In MDR gram-negative bacteria, AuNPs cause a loss of the membrane potential by decreasing adenosine triphosphate (ATP) through ATPase inhibition and by preventing ribosomal binding to transfer RNA (tRNA).

We are currently moving towards green synthesis of AuNPs, through the use of plants, fungi, bacteria and viruses as a source for reducing and stabilizing agents necessary for synthesis[43]. Green AuNP synthesis is also preferred because the NPs obtained by this method show higher antibacterial activity compared with those produced by chemical synthesis methods[44]. For example, Nayem et al[43] used *Amorphophallus paeoniifolius* tuber extract as a bio-reducing agent thanks to the presence of alkaloids, steroids, carbohydrates and proteins. Indeed, these compounds allow the reduction of metal ions and colloidal stabilisation[45,46]. MubarakAli et al[47] biosynthesized AuNPs starting from plant extracts of *Mentha piperita* leaves, with strong bactericidal activity against *Escherichia coli* and *S. aureus*. Vijayan et al[48] used extracts of *Indigofera tinctoria*, and the NPs they synthesized exhibited strong antimicrobial activity against *S. aureus, Bacillus pumilis, E. coli, Pseudomonas spp., Aspergillus niger* and *Aspergillus fumigatus*. AuNPs can also be biosynthesized from *Abelmoschus esculentus*[49]. Sathiyaraj et al[38] demonstrated how it is possible to synthesize AuNPs using Panchgavya, a combination of five products of bovine origin: urine, dung, milk, curd and ghee (which are rich in beneficial microorganisms, carbohydrates, proteins, lipids, micronutrients and antioxidants). The bacterial activity of these NPs was high against gram-negative bacteria (*E. coli* and *Klebsiella pneumoniae*) and moderate against gram-positive bacteria (*Bacillus subtilis*). This further confirms the possibility of using biological methods to synthesize NPs with antibacterial activity.

Iron nanoparticles

When functionalized, iron nanoparticles (FeNPs) show antimicrobial properties. In fact, they are generally inert in their native form, while modifications of their surfaces, as well as their oxidation, give them both non-stick and antibacterial properties[3]. Beyth et al[50] observed that FeNPs inhibited bacterial biofilms formed by gram-negative and gram-positive bacterial isolates. Chemically synthesized FeNPs are generally biologically compatible and, according to Aparicio-Caamaño et al[51], their conjugation with an antibiotic drug (e.g., erythromycin) enhances the antibacterial effect against *Streptococcus pneumoniae*. Similarly, conjugation of FeNPs with tobramycin and alginate enhances the antibacterial effect against *P. aeruginosa*. These conjugations also inhibit the formation of biofilms and, therefore, are proposed as a low-cost alternative to any antibacterial coatings[52]. In recent years, there have been published papers in which the authors discuss green synthesis of these NPs. For example, Batool et al[53] showed how it is possible to synthesize FeNPs using *Phoenix dactylifera* extract as a reducing agent and iron sulphate heptahydrate as a substrate. These NPs showed maximum antimicrobial activity on *E. coli* and *K. pneumoniae*.

Silver nanoparticles

Historically, Ag has been used as an antimicrobial agent alone or in combination. This metal is present, in combination with other substances, in creams and dressings for the treatment of burns and ulcers, in food packaging and it is used in various industries[54-56]. AgNPs range in size from 1 to 100 nm and show strong antibacterial properties against gram-negative and gram-positive bacteria, including MDR strains, and a higher surface-to-volume ratio than Ag in its bulk form[57]. AgNPs have shown[58] antimicrobial activity against a variety of MDR pathogenic microorganisms. These AgNPs can be used to manufacture surgical instruments, catheters and drugs[59,60]. The potential of AgNPs as antimicrobial agents is linked to their various mechanisms of action. Indeed, they act by damaging various vital bacterial structures; hence, they have the ability to kill various types of bacteria[61]. The mechanism by which they exert toxicity is not entirely clear. What is certain is the release of Ag ions that, upon entering the cell, lead to the production of ROS and highly reactive nitrogen radicals (RNS), which oxidize cell structures,

Table I. Classification of NPs with antimicrobial activities.

Types of NPs	Size and shape	Main target	Mechanism of action
Inorganic NPs			
Metal-based NPs			
Gold (Au) NPs	21 nm; hexagonal	MRSA, *E. coli, Pseudomonas spp., K. pneumoniae, Bacillus subtilis Aspergillus niger, Aspergillus fumigatus*	Making holes in the cell wall. Inhibition of the transcription process due to the bind to the DNA.
Iron (Fe) NPs	10-20 nm; spherical	*S. aureus, S. epidermidis, E. coli*	ROS production and oxidative stress.
Silver (Ag) NPs	5-50 nm; spherical	*P. aeruginosa, V. cholerae, K. pneumoniae, S. aureus, E. faecium, S. epidermidis*	Separation of the cytoplasmic membrane from the cell wall, plasmolysis, inhibition of the DNA replication and respiratory chain.
Metal oxide-based NPs			
Copper oxide (CuO)	12 nm; spherical	*B. subtilis, S. aureus, E. coli*	Reduction of the cell wall. Alteration of biochemical processes.
Titanium oxide (TiO_2)	17 nm; hollow nanospheres	*E. coli, S. aureus, several fungi*	ROS production and DNA damage.
Iron oxide (Fe_2O_3)	10-20 nm; spherical	*S. aureus, S. epidermidis, E. coli*	ROS production and oxidative stress.
Zinc oxide (ZnO)	28 nm; wurtzite shape	*E. coli, Listeria monocytogenes, Salmonella, S. aureus*	ROS production with cellular damage for oxidative stress.
Magnesium oxide (MgO) NPs	27 nm; spherical	*S. aureus, E. coli, Bacillus megaterium, Bacillus subtilis*	ROS production with lipid peroxidation, alkalizing effect.
Cerium oxide (CeO)	Spherical-shaped, nanocubs, nanosheets	*E. coli, S. aureus, K. pneumoniae*	Altered functionality of plasmatic membrane, ROS production, alteration of the electronic flow and of the transport of nutrients
Other NPs			
Yttrium floride (YF)	Needle-like (length of 342 ± 51 nm and a width of 52 ± 12 nm)	*E. coli, S. aureus*	Binding and inhibition of enzymes containing metal functional groups
NO-releasing silica	Spherical-shaped, 136 ± 15 nm	*P. aeruginosa, E. coli, S. aureus, S. epidermidis*	ROS production
Ceramic NPs	Amorphous, porous, or polycrystalline	*P. aeruginosa, E. coli, E. faecalis, S. aureus*	Release of Sm^{3+} ions that can cause damage to bacterial wall and DNA; ROS production with cellular damage for oxidative stress
Semiconductor NPs	CdS and ZnS: spherical shape and variable size (10-65 nm)	*Streptococcus spp., Staphylococcus spp., Lactobacillus spp., K. pneumoniae*	Discharge of ions, which react with the thiol groups of the proteins present on the bacterial cell membrane
Carbon-based NPs			
Graphene	Honeycomb lattice	*E. coli, S. aureus, S. mutans*	Alteration of membrane integrity and inducing of oxidative stress by electron transfer
Fullerenes	Hollow, spherical molecules; single-layer (diameters up to 8.2 nm) or multilayer (diameters from 4 to 36 nm)	*E. coli, S. aureus, P. aeruginosa*	Inhibition of energy metabolism following their internalization and-induction of cell membrane rupture
Carbon-nanotubes	Hollow cylinder; SWCNTs (diameter of 1 to 7 nm), and MWCNTs (diameter ranging from 10 to 20 nm)	*E. coli, B. subtilis*	Interaction with the bacterial surface; ROS production and oxidation of membrane components
Organic NPs			
Chitosan	Linear polycationic heteropolysaccharide	*E. coli, K. pneumoniae, P. aeruginosa, S. aureus*	Alteration of transmembrane transport and membrane permeability. Inhibition of DNA replication.

biomolecules, and the enzymes of the respiratory chain (with a consequent decrease in the level of ATP), with DNA denaturation, lipid peroxidation and finally cell death[62]. Furthermore, Ag ions can

bind various biomolecules and membranes, altering the integrity of the latter[63].

AgNPs, along with other nanomaterials, have been studied[64] in the post-antibiotic era to identify new agents that could help the fight against pathogenic microorganisms without favoring the emergence of new resistance. In this case, AgNPs are an excellent alternative as they have proven efficacy in both the decontamination of medical supplies and in the treatment of ongoing infections[65]. They can also be conjugated to antibiotics, often showing a synergistic effect[57]. In the last 15 years, more than 500 tons of AgNPs have been produced each year[66]. Alongside the classical chemical synthesis of AgNPs, there has been recent attention regarding synthesizing AgNPs through biological approaches such as green synthesis or photosynthesis[67]. In this method, Ag ions are converted into AgNPs using secondary metabolites from vegetables in a single-stage reaction; no surfactants or other stabilizing compounds are used[68]. For example, Foroohimanjili et al[69] showed how it is possible to photosynthesise AgNPs by using *Mespilus germanica* extract. The AgNPs show an antimicrobial, anti-biofilm and anti-quorum-sensing effects on clinical MDR *K. pneumoniae* strains. Several plant extracts have been reported[70,71] for the synthesis of AgNPs. Kumar et al[70] synthesized spherical AgNPs using an aqueous mixture of *Alternanthera dentate* extract, which showed potential antimicrobial activity against *E. coli, Enterococcus faecalis, P. aeruginosa* and *K. pneumoniae*. Another study[71] highlighted how it is possible to biosynthesize AgNPs with antibacterial activity using an extract of Lycopersicon esculentum. These AgNPs have a bacteriostatic effect against E. coli at the lowest concentrations but are bactericidal at the highest concentration.

Metal Oxide-Based Nanoparticles

The oxidation of the metals usually used for NP synthesis modifies their properties, making them more reactive[72]. CuO, TiO_2, iron oxide (Fe_2O_3), zinc oxide (ZnO) and MgO are commonly used to produce metal oxide-based NPs.

Copper oxide nanoparticles

CuO has shown excellent antibacterial activity against Gram-positive and Gram-negative bacteria[73]. For this reason, it is used as an antibacterial coating on various substrates, especially medical equipment. Considering that $CuSO_4$ and $Cu(OH)_2$, aqueous solutions of Cu, complex copper species or copper-containing polymers act as antibacterial compounds[74]. The U.S. Environmental Protection Agency (EPA) has registered[75,76] Cu as the only metal with strong antimicrobial properties, as it inhibits the growth of 99.9% of pathogens within 2 hours.. Non-oxidised NPs already show high antibacterial efficacy thanks to the interaction between the bacterial cell membrane and CuNPs, which results in lipid peroxidation, oxidation and denaturation of proteins, and interaction with phosphorus and sulphur and with the compounds that contain them, leadings to DNA degradation and eventual death[77]. A synergistic effect between CuNPs and antibiotics, such as erythromycin, azithromycin and norfloxacin, has also been documented[78]. CuONPs have proved[17] to have excellent anti-biofilm activity and are capable of blocking ATP synthesis and can rapidly lead to the death of bacterial cells. Nithiyavathi et al[73] demonstrated that CuONPs can be synthesized using almond gum as a reducing agent; the resulting NPs exhibit excellent antibacterial activity against gram-positive and gram-negative bacteria. Other studies[79,80] have been conducted on the biosynthesis of CuNPs. For example, it has been possible to synthesize stable CuNPs (variable size of 40-100 nm) using *Magnolia virginiana* leaf extract treated with water $CuSO_4 \cdot 5H_2O$ solution as a reducing agent, and these showed[79] excellent antibacterial potential. *Citrus medica* Linn extract has also been used[80] to biosynthesize CuNPs (size 10-60 nm), and these were then tested on some bacterial strains, showing antibacterial activity against *K. pneumoniae, E. coli, S. aureus, Proteus vulgaris, Salmonella typhi, Shigella flexneri, Propionibacterium acnes, P. aeruginosa* and *E. faecalis*. Ren et al[81] reported increased sensitivity of *E. coli* and *E. faecalis* to CuONPs.

Titanium dioxide nanoparticles

Titanium (Ti) and its alloys are widely used in orthopedics and dentistry for their unique mechanical properties, namely 1) resistance to corrosion in biological media, 2) biocompatibility and 3) capacity of bone integration. The only drawback of Ti itself is that it is highly susceptible to microbial colonisation[82]. However, TiO_2NPs exhibit anti-biofilm and antimicrobial properties due to their size and stability. These properties are linked to their ability to cross the bacterial cell wall and to interact with the cell membrane. Khashan et al[83] showed an inhibitory effect in *P. aeruginosa, A. baumannii, K. pneumoniae, E. coli* and *S. typhi*. Numerous studies[84] have also showed the ability

of TiO_2NPs, prepared by the sol-gel method, to act against MDR strains of *P. aeruginosa* isolated from clinical specimens, as well as to interfere with the important bacterial communication mechanism, namely quorum sensing (essential for biofilm production), and with a resistance mechanism, such as efflux pumps. TiO_2NPs are also capable of potentiating the effect of antibiotics. Ahmed et al[85] reported a reduction in antimicrobial resistance in MDR strains when treated with TiO_2NPs and antibiotics. This is probably due to a synergistic effect. For this reason, TiO_2NPs are currently used in many fields, such as the pharmaceutical (as vehicles for drug delivery), food and cosmetics industries. Moreover, these NPs are often used to purify environmental matrices (air and water) or as coatings of biomedical devices[17].

Zinc oxide nanoparticles

ZnO is a semiconductor metal oxide that has aroused great interest in the scientific community due to its low-cost production, ease of preparation and safety[86]. From there, it was a short step to the synthesis of zinc oxide nanoparticles (ZnONPs). They have a great antimicrobial capacity, which depends on their size, shape and eventual functionalization. Xie et al[87] demonstrated that smaller ZnONPs have greater bactericidal power due to a first interaction between the NPs and the bacterial membrane. This interaction increases membrane permeability, with the consequent entry of ZnONPs into the intracytoplasmic environment. This phenomenon increases ROS levels and oxidative stress, which first inhibit the growth of microorganisms and, if prolonged, lead to their death. Zn ions are also important in the antibacterial action: once released, they diminish mitochondrial activity and, therefore, promote cell death[17]. Their antibacterial efficacy has been studied[88] and highlighted in several pathogenic bacterial species, such as *S. aureus, E. coli* and methicillin-resistant *S. aureus* (MRSA). To date, ZnO coatings are used for their undisputed antibacterial efficacy for food packaging, as in this context it is essential to maintain food safety and to extend the shelf-life of the product[89].

Magnesium oxide nanoparticles

MgONPs are more attractive for human administration than other NPs because they can be metabolized within the body, resulting in the release of hydroxide and Mg ions, which are easily eliminated. These NPs exert antibacterial activity against *E. coli, P. aeruginosa, K. pneumoniae, Staphylococcus epidermidis* and *S. aureus*[17,90]. Nguyen et al[91] showed that MgONPs with a diameter of 20 nm had a bactericidal effect against gram-negative strains and bacteriostatic effect against gram-positive strains, and mortality was not influenced by alkalizing effect. The antibacterial effect could result from 1) ROS production (not balanced by the action of cellular antioxidant systems), 2) release of calcium ions in the cell broth (related to the increase in Mg ions in the medium) and 3) the ability of these NPs to destroy the bacterial wall and subsequently to undermine the integrity of the plasma membrane[91]. Hayat et al[90] confirmed the third hypothesis. They demonstrated how spherical MgONPs, with a diameter of 50-70 nm, caused the rupture of bacterial membrane. In addition, they highlighted an anti-adhesive capacity with an anti-biofilm effect.

Cerium oxide nanoparticles

Cerium (Ce) is one of the most abundant lanthanides in Earth's crust and can be found in two different oxidation states: Ce^{3+} and Ce^{4+} (more stable). This makes it possible to form two different oxides, namely cerium dioxide (CeO_2) and cerium sesquioxide (Ce_2O_3). Cerium oxide nanoparticles (CeONPs) are produced with the sol-gel method, which uses cerium (III) nitrate hexahydrate and ammonium hydroxide as precursors, with the use of different solvents[92], but it can also happen with other methods. Dhall and Self[93] listed other synthesis methods such as solution precipitation, hydrothermal, solvo-thermal, ball milling, thermal decomposition, spray pyrolysis and thermal hydrolysis. In the same study[93], the authors discussed possible synthesis mediated by green plants, fungi and some nutrients. Kannan and Sundrarajan[94] provided an example of phytosynthesis. They showed that Acalypha indica leaf extract is used to give rise to large relative CeONPs, which are currently not appropriate for biomedical application. Munusamy et al[95] used mycosynthesis with *Curvularia lunata* to make smaller CeONPs. Kargar et al[96] reported about nutrient-mediated synthesis in which they used egg white as a substrate to synthesize small CeONPs.

CeONPs are a promising tool for tissue regeneration and healing of soft tissues, thanks to their antioxidant, anti-inflammatory, antiapoptotic, antibacterial and angiogenic properties[97]. For these reasons, they are also considered inorganic antioxidants with catalytic activity similar to that of superoxide dismutase (SOD) and catalase[98], due

to the self-regeneration of their surface based on redox cycling between Ce^{3+} and Ce^{4+}, in response to their surrounding environment[93]. According to Qi et al[97], CeONPs are effective against gram-positive and gram-negative bacteria. There are three mechanisms: 1) direct contact between CeONPs and bacterial membranes, whose functionality is altered; 2) triggering ROS production, which causes damage to various biological macromolecules (nucleic acids, proteins, polysaccharides and lipids); and 3) link to the external membrane that modify the electronic flow and, therefore, the transport of nutrients. Kalaycıoğlu et al[99] confirmed the antibacterial activity of CeONPs. Composite films of chitosan and cellulose acetate containing CeONPs showed antibacterial activity against *E. coli* and *S. aureus*. The antibacterial activity was directly proportional to the quantity of CeONPs present in the films. In addition to this activity, CeONPs also exhibit synergistic activity in combination with β-lactam antibiotics against MDR *K. pneumoniae*[100].

Other Inorganic Nanoparticles

Yttrium fluoride nanoparticles

Yttrium fluoride-based (HF) NPs have been produced due to the well-known antibacterial activity of fluorides. In fact, F-/HF can bind to enzymes containing metal functional groups (Al and Be), such as the haem group[101,102]. Furthermore, fluorine is an important inhibitor of glycolysis[102]. Lellouche et al[103] synthesized YF3 needle-like NPs using sono-chemical irradiation and starting from an aqueous solution of yttrium acetate tetrahydrate and HF. These NPs exhibited both antibacterial and anti-biofilm activity against *E. coli* and *S. aureus*.

Nitric Oxide-Releasing Silica Nanoparticles

The idea of synthesizing nitric oxide (NO)-releasing silica NPs arises from the awareness of the antimicrobial properties of NO[104] produced by immune cells during inflammatory processes and acting as a reactive free radical. Raulli et al[105] demonstrated the efficacy of these NPs on both gram-positive and gram-negative bacteria, while Ghaffari et al[106] showed the same effect on MRSA. Hetrich et al[107] reported that NO-releasing silica NPs showed a bactericidal effect on *P. aeruginosa*. In addition to the bactericidal effect, other studies[108] have shown that these NPs possess an anti-biofilm effect on *P. aeruginosa, E. coli, S. aureus* and *S. epidermidis*.

Ceramic nanoparticles

Ceramic NPs comprise carbonates, phosphates and oxides of metals and metalloids, such as silica, aluminium, Ti and calcium[109,110]. They are synthesized through heat and subsequent cooling. Their structure can be amorphous, porous or polycrystalline[111]. They are mainly used in the biomedical field thanks to their high stability and load capacity[112]. In fact, these particles can be used to trap proteins, enzymes and drugs inside them, which will thus be conveyed and protected by the denaturing effects of pH and temperature[113]. Ciobanu et al[114] synthesized and characterized samarium NPs doped with hydroxyapatite. The authors started from the premise that hydroxyapatite is a biocompatible, bioactive and osteoconductive material and that samarium ions (Sm^{3+}) possess antibacterial activity. They tested these NPs against *P. aeruginosa, E. coli, E. faecalis* and *S. aureus*. They had an antibacterial effect against both gram-positive and gram-negative bacteria, although it was dependent on the samarium concentration. Furthermore, the NPs are biocompatible and therefore excellent for application in the biomedical field. Iconaru et al[115] hypothesized three different mechanisms underlying the antibacterial effect of samarium NPs: 1) interactions between ions and the bacterial wall (with consequent damage of cellular integrity); 2) ROS generation; and 3) release of Sm^{3+} ions that can cause damage to bacterial DNA.

Semiconductor nanoparticles

Semiconductor NPs are made with materials that have properties halfway between metals and nonmetals, and their properties change significantly when the band gap is optimized compared with bulk semiconductor materials[111]. For example, Malarkodi et al[116] synthesized cadmium sulphide (CdS) and zinc sulphide (ZnS) NPs of spherical shape and variable size (10-65 nm) with green methods. They tested the antibacterial effect of different concentrations against K. pneumoniae and oral pathogens (*Streptococcus spp., Staphylococcus spp.* and *Lactobacillus spp.*). Both CdS and ZnS NPs showed antimicrobial activity on the tested strains. For this reason, these NPs could be used to prevent the growth of oral pathogens.

Carbon-Based Nanoparticles

Carbon-based NPs are completely made of carbon[20]. In addition to causing mechanical da-

mage, carbon nanostructures appear to be able to promote strong ROS generation[117]. The collective damage is presumably the cause of the antibacterial effect exhibited by carbon-based NPs[118]. Carbon-based NPs can be classified into fullerenes, graphene, carbon nanotubes (CNTs), carbon nanofibers and carbon black[20].

Fullerenes

Fullerenes are hollow, closed (spherical) molecules, characterized by a symmetrical closed-cage structure made up of carbon atoms held together by sp^2 hybridization. These carbon atoms arrange themselves into hexagonal and pentagonal rings, forming single-layer (diameters up to 8.2 nm) or multilayer structures (diameters from 4 to 36 nm). Fullerene C_{60} is the most famous and best known of all fullerenes in which the carbon atoms are arranged to form a soccer ball-like structure[119]. Fullerenes exert antimicrobial activity *via* two modalities: inhibition of energy metabolism following their internalisation[120] and induction of cell membrane rupture[121]. This antimicrobial activity is effective against *E. coli, S. aureus,* and *P. aeruginosa*[122]. Moreover, this activity is more pronounced against gram-positive bacteria owing to their higher membrane permeation[123].

Some studies[124] have shown how it is possible to combine the activity of fullerenes with that of some nanocompounds. For example, Alekseeva et al[125] found that fullerene-filled polystyrene films had antibacterial activities against *S. aureus* and *E. coli*. The antimicrobial activity was not present in the plastic polymer alone, so the authors hypothesized that the reason for the microbial inactivation is the interaction of fullerenes with the protein amino acids in bacteria, causing damage to the cell membrane.

Graphene

Graphene is an allotrope of carbon, made up of carbon atoms arranged on a flat two-dimensional surface, forming a honeycomb lattice. Generally, the thickness of the graphene sheet is equivalent to the size of a single atom. The antimicrobial activity of graphene-containing nanomaterials is derived from their ability to alter membrane integrity and to induce oxidative stress by electron transfer[126]. The bacteriostatic activity of graphene, whether oxidized or not, has been demonstrated[127] against *E. coli*, and this is probably due to the direct contact between this material and the plasma membrane[128]. The same effects have also been observed in various forms of graphene NPs. However, there are limitations in the use of graphene - for example, its tendency to agglomerate due to its poor dispersion in water[129]. Therefore, to improve its properties, it is often oxidized, obtaining graphene oxide (GO). From GO, it is possible to obtain reduced graphene oxide (rGO) by chemical or thermal reduction. Bacali et al[130], highlighted how the polymethylmethacrylate matrix, widely used in dentistry, filled with 1% and 2% by weight of Ag and GO NPs showed strong antimicrobial action against *S. aureus, E. coli* and *Streptococcus mutans.*

Carbon Nanotubes

Carbon Nanotubes (CNTs) are synthesized from a graphene nanosheet that is wrapped around hollow cylinders. Based on the number of rolled sheets, we refer to single-walled carbon nanotubes (SWCNTs), with a diameter of 1-7 nm, and multi-walled carbon nanotubes (MWCNTs), with diameters ranging from 10 to 20 nm. The carbon atoms that make up the walls of the CNTs possess sp^2 hybridization, which generates a cloud of delocalized electrons along the wall[131]. The ends of these nanotubes may or may not be closed by a half molecule of fullerene. Currently, CNTs are widely used in many industrial fields (engineering, informatics, aerospace, etc.) and, for this reason, their potential toxicity to humans and the environment has been studied[132-137].. CNTs seem to have even greater antimicrobial activity than fullerenes, deriving from their ability to interact with the bacterial surface and to cause damage and oxidation of membrane components, as well as to induce massive ROS production in bacteria. This antibacterial activity is dependent on the diameter, length, surface chemistry, electronic structure, residual catalyst and surface functional groups[138]. Demonstrating the importance of CNT size, Kang et al[139] studied the antibacterial effects of SWCNTs and MWCNTs on *E. coli*, showing that SWCNTs were much more toxic than MWCNTs, as they were more able to interact and penetrate the cell wall. Therefore, in general, shorter nanotubes with a smaller diameter have a greater antibacterial effect[140]. However, the situation changes when considering liquid solutions. In this case, larger CNTs have a greater antibacterial effect, probably due to their lower tendency to aggregate and, therefore, their greater bio-efficacy[141]. Furthermore, due to their nature, they seem to have greater efficacy on spherical-shaped bacteria compared with rod-shaped

bacteria[138]. In addition, functionalized SWCNTs with -OH, -COOH and other surface groups exhibit better antimicrobial activity against both gram-positive and gram-negative bacteria[142], inducing wall damage and releasing the DNA content. In a previous study[143], the authors showed that the antibacterial activity of MWCNTs seems to be linked with the antibiotic-resistance of bacterial strains. CNTs can also be conjugated with Ag, ZnO and CuO NPs. Conjugation results in a great synergistic effect[144-146]. SWCNTs also show[138] anti-biofilm activity, acting with a bactericidal effect on sessile forms of *E. coli* and *B. subtilis*[147], especially when exposure occurs during the early stages of biofilm formation. This phenomenon can be explained because SWCNTs act as anti-adhesives thanks to their mobility, creating an unstable substrate. This effect is greater for larger SWCNTs.

Organic Nanoparticles

Organic NPs consist of proteins, carbohydrates, lipids and polymers[148]. Some examples are dendrimers, protein complexes (ferritin), micelles and liposomes. These NPs are biodegradable, non-toxic and sensitive to heat and electromagnetic radiation[19]. These characteristics have led to extensive investigation of these NPs for drug delivery, especially for cancer therapies[19,149]. A particular use of these particles is in vaccinology as carriers and/or adjuvants of antigens (nanovaccinology)[150].

Chitosan Nanoparticles

Chitosan is a linear polycationic heteropolysaccharide compound of *N*-acetyl D-glucosamine and D-glucosamine units obtained by partial alkaline *N*-deacetylation of chitin[151] which occurs naturally in the shells of crustaceans, such as crabs, shrimps and lobsters[152]. Recently, some studies[153] have indicated the possibility of producing chitosan from mushrooms. The main characteristics of chitosan are its biocompatibility, biodegradability and the total absence of toxicity. Nevertheless, it still shows antimicrobial effects, and this made it an ideal candidate for human use. The antimicrobial effects of chitosan are attributed to its positive surface charges, which allow it to interact with the negatively charged bacterial wall. This interaction alters transmembrane transport and membrane permeability - and thus alters homeostasis in bacterial cells. Furthermore, binding to bacterial DNA is possible, causing inhibition of DNA replication and, subsequently, cell death[154]. Chitosan can also exert antibacterial activity *via* its ability to act as a chelating agent. For example, binding to trace metal elements can lead to the production of toxins that inhibit microbial growth[155]. As previously stated, chitosan has a wide range of applications. In the medical field, it is integrated into bandages to promote both the wound healing process through the stimulation of fibroblasts, and for its antibacterial properties; it is also used in orthopedic tissue engineering[156]. Much research[154] has focused on the development of chitosan-based systems for antimicrobial efficacy and also for food packaging. Chitosan NPs have been widely used to improve the internalization of antibiotics[157]. In some cases, these chitosan NPs also enhance the action of the antibiotic itself. Jamil et al[158] tested chitosan NPs loaded with cefazolin against *E. coli, K. pneumoniae* and *P. aeruginosa* and showed greater bacterial activity than that of the antibiotic alone. The same results were also obtained for vancomycin against drug-resistant *S. aureus*[154]. However, there are contradictory results from some studies carried out on the efficacy of chitosan NPs alone as antimicrobial agents. According to Sadeghi et al[159], the effects of chitosan NPs on *S. aureus*, compared with the free soluble polymer, were minor. On the other hand, Kong et al[160] found that chitosan NPs had greater antibacterial activity than chitosan.

Possible Practical Biomedical Applications of Nanoparticles in Reducing the Occurrence of Healthcare-Associated Infections

Personal Protective Equipment Coated with Nanoparticles

Considering the anti-microbial potential of NPs, it has been possible to develop nanomaterials to prevent bacterial adhesion and biofilm formation on medical devices. Medical devices with added NPs are inexpensive, biocompatible, and potentially able to reduce the onset of HAIs. One of the most important steps to reduce HAIs is to counteract cross-contamination of the hospital environment with pathogens; this is possible through the use of ad hoc personal protective equipment (PPE). For example, Bhattacharjee et al[161] highlighted the antimicrobial efficacy of cotton/silk tissues containing rGO and Ag/CuNP fibres: incorporation of both produced a synergistic effect. In fact, rGO NP complexes,

incorporated into cotton or silk, reduced *E. coli* and *P. aeruginosa* viability by about 99% and *S. aureus* viability by 78-99%. Furthermore, it is important to underline that there was not a substantial decrease in viability (> 30%) in mammalian cells (HEK-293), highlighting the good biocompatibility of these materials. For these reasons, incorporating NPs into cotton or silk can be an excellent method to produce protective clothing such as gowns for healthcare personnel. Antibacterial NPs can also be added to face masks, which are also crucial PPE. Hiragond et al[162] showed that face masks coated with colloidal AgNPs exerted antimicrobial activity against *S. aureus* and *E. coli*. In this way, it has been shown how this type of masks can be useful in health settings.

In Vivo Use of Nanoparticles

Kalita et al[163] showed that lysozyme coated AuNPs in combination with ampicillin had excellent antibacterial power against *S. aureus, Acinetobacter calcoaceticus, P. aeruginosa, E. coli, K. pneumoniae, B. subtilis* and *Bacillus cereus*. Furthermore, intraperitoneal and topical administration of these hybrid NPs eradicated MRSA infection at the lymphatic and local levels in the presence of a diabetic rat wound. These antibacterial effects were accompanied by total biocompatibility *in vivo*. For these reasons, these composite NPs would seem an excellent adjuvant for the healing of diabetic wounds. The same application is also possible for insoluble fur keratin-derived powder containing silver nanoparticles (FKDP-AgNPs). Konop et al[164] demonstrated its absolutely biocompatibility *in vivo* and, at the same time, its antimicrobial effect in the allogenic full-thickness surgical skin wound model in diabetic mice. In fact, this nanomaterial did not cause an inhibition of the growth of fibroblasts or hemolysis and had an antibacterial effect against *E. coli* and *S. aureus*. For these reasons, its application to facilitate tissue restoration and the healing of infected wounds is desirable. Another idea would be to use bacterial cellulose with healing properties, loaded with AgNPs by loading them in bacterial cellulose hydrogels with moist healing properties. This AgNP hydrogel showed high cytocompatibility and antimicrobial activity against *S. aureus* and *P. aeruginosa*[165]. Another material useful for healing diabetic foot ulcers is Ag-ZnO-loaded carboxymethyl cellulose/K-carrageenan/graphene oxide/konjac glucomannan hydrogel, which showed broad bactericidal effect against *S. aureus* and *E. coli*[166]. Moreover, its good cytocompatibility has also been demonstrated through *in vitro* tests, while accelerated re-epithelialization was also found through *in vivo* tests[166].

Moreover, to repair infected bone and therefore facilitate the formation of a fibro-cartilaginous callus and the killing of infecting bacteria, a collagen scaffold encapsulating AgNPs and bone morphogenetic protein 2 (BMP-2) can be used[167]. This material exhibits high osteoconductivity and an antibacterial effect against MRSA. Another option for promoting removal/preventing infections in the orthopedic field is to use particular microspheres, called COS-Ag-Alg-HA, containing chitooligosaccharide (COS) coated with AgNPs, alginate (Alg) and hydroxyapatite (HA) as bone graft substitutes. Dalavi et al[168] tested cytocompatibility using MG-63 cells; the antimicrobial effect exerted by this material was directed against *S. aureus.* To combat some implant infections, it could be useful to use dextran/CeO_2 NPs which have shown[169], in addition to biocompatibility, an antibacterial effect against *P. aeruginosa* and *S. epidermidis.*

Medical Devices Coated with Nanoparticles

In cardiology, an additional precaution to prevent bacterial infections of heart valves that could lead to endocarditis is the use of pyrolytic carbon coated with a film of AgNPs as an artificial heart valve. This film showed[170] antibacterial activity against MRSA, *Streptococcus pyogenes, E. coli, K. pneumoniae, P. aeruginosa* and *P. vulgaris*. Another strategy for preventing nosocomial infections is to coat surfaces, implantable prostheses, and medical devices with antimicrobial films also capable to prevent the formation of microbial biofilm. Self-assembled monolayers (SAMs) and multilayer films fall into this category of antimicrobial films. The action of these coatings can be anti-adhesive or anti-biofilm[171,172]. The anti-adhesive films are divided into hydrophilic, super-hydrophilic and slip surfaces according to the mechanism of action. Bactericidal films, on the other hand, perform their function either through the release of toxic ions or through the interaction between antimicrobial agents and bacterial cells[173]. SAMs are monolayers (1-5 nm) that can prevent bacterial adhesion by increasing surface hydration or can prevent biofilm formation by disrupting quorum sensing[174]. SAMs can be loaded with a wide range of molecules, including NPs. There are many studies[175-180] on the grafting of NPs on a SAM, especially Ag and copper sulphide NPs, that have shown the applicability of these films thanks to their antibacterial and

anti-biofilm activity against *E. coli, Micrococcus luteus, S. aureus* and *S. epidermidis*. This finding is very important, considering that these bacterial strains are often responsible for infections in breast implants[181-183], central venous catheters[184], cochlear implants[185], endotracheal tube[186,187], feeding tube[188], orthopedic implants[189,190], stents[191] and urinary catheters[192]. Multilayers can also be loaded with AgNPs. For example, Bao et al[173] synthesized an aPOX-AgNP multilayer film, consisting of a hydrophilic anti-adhesive portion and a bactericidal loaded portion loaded with AgNPs. This multilayer film could also be applied to coat implantable devices thanks to its sensitivity to pH in the release of Ag ions.

Conclusions

HAIs are currently one of the main challenges of modern public health, especially due to the increasingly widespread phenomenon of antibiotic resistance. For this reason, many alternative strategies are under study - and the potential use of NPs and nanomaterials with intrinsic antimicrobial properties is one of the most studied. Producing surfaces and devices capable of counteracting and avoiding microbial adhesion and especially the proliferation and the biofilm formation could represent a cornerstone in this difficult fight. Many researchers have highlighted the manageability and the ductility of these materials, used by many different industrial fields[193]. Excellent antimicrobial properties have been found for different NPs. However, further investigation, especially of biocompatibility, is necessary to evaluate the effective possibility to use these materials.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Availability of Data and Materials

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Authors' Contributions

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References

1) Stewart S, Robertson C, Pan J, Kennedy S, Dancer S, Haahr L, Manoukian S, Mason H, Kavanagh K, Cook B, Reilly J. Epidemiology of healthcare-associated infection reported from a hospital-wide incidence study: considerations for infection prevention and control planning. J Hosp Infect 2021; 114: 10-22.
2) Awad HM, Kamal YES, Aziz R, Sarmidi MR, El-Enshasy HA. Antibiotics antimicrobial secondary metabolites: Production and application. J Teknol 2012; 59: 101-111.
3) Spirescu VA, Chircov C, Grumezescu AM, Vasile BȘ, Andronescu E. Inorganic Nanoparticles and Composite Films for Antimicrobial Therapies. Int J Mol Sci 2021; 22: 4595.
4) Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, Scheld M, Spellberg B, Bartlett J. Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America. Clin Infect Dis 2009; 48: 1-12.
5) Medina E, Pieper DH. Tackling Threats and Future Problems of Multidrug-Resistant Bacteria. Curr Top Microbiol Immunol 2016; 398: 3-33.
6) Elemam A, Rahimian J, Mandell W. Infection with Panresistant Klebsiella pneumoniae: A Report of 2 Cases and a Brief Review of the Literature. Clin Infect Dis 2009; 49: 271-274.
7) Behzadi P, Baráth Z, Gajdács M. It's Not Easy Being Green: A Narrative Review on the Microbiology, Virulence and Therapeutic Prospects of Multidrug-Resistant Pseudomonas aeruginosa. Antibiotics 2021; 10: 42.
8) Mitevska E, Wong B, Surewaard B, Jenne C. The Prevalence, Risk, and Management of Methicillin-Resistant Staphylococcus aureus Infection in Diverse Populations across Canada: A Systematic Review. Pathogens 2021; 10: 393.

9) Sarshar M, Behzadi P, Scribano D, Palamara A, Ambrosi C. Acinetobacter baumannii: An Ancient Commensal with Weapons of a Pathogen. Pathogens 2021; 10: 387.

10) Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. BMC Infect Dis 2006; 6: 130.

11) Otter JA, Yezli S, French GL. The role played by contaminated surfaces in the transmission of nosocomial pathogens. Infect Control Hosp Epidemiol 2011; 32: 687-699.

12) Facciolà A, Pellicanò GF, Visalli G, Paolucci IA, Venanzi Rullo E, Ceccarelli M, D'Aleo F, Di Pietro A, Squeri R, Nunnari G, La Fauci V. The role of the hospital environment in the healthcare-associated infections: a general review of the literature. Eur Rev Med Pharmacol Sci 2019; 23: 1266-1278.

13) Munita JM, Arias CA. Mechanisms of Antibiotic Resistance. Microbiol Spectr 2016; 4: 34-57.

14) Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol 2018; 4: 482-501.

15) Morrison L, Zembower TR. Antimicrobial Resistance. Gastrointest Endosc Clin N Am 2020; 30: 619-635

16) Center for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States. 2019. Available online: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

17) Fatima F, Siddiqui S, Khan WA. Nanoparticles as Novel Emerging Therapeutic Antibacterial Agents in the Antibiotics Resistant Era. Biol Trace Elem Res 2021; 199: 2552-2564.

18) Kheiri S, Liu X, Thompson M. Nanoparticles at biointerfaces: Antibacterial activity and nanotoxicology. Colloids Surf B Biointerfaces 2019; 184: 110550.

19) Joudeh N, Linke D. Nanoparticle classification, physicochemical properties, characterization, and applications: a comprehensive review for biologists. J Nanobiotechnology 2022; 20: 262.

20) Ealia SAM, Saravanakumar MP. A review on the classification, characterisation, synthesis of nanoparticles and their application. In: IOP Conference Series: Materials Science and Engineering. IOP Publishing 2017; 32019.

21) Kolahalam LA, Viswanath IVK, Diwakar BS, Govindh B, Reddy V, Murthy YLN. Review on nanomaterials: synthesis and applications. Mater Today Proc 2019; 18: 2182-2190.

22) Chaitanya Kumari S, Vivek Dhand, P. Naga Padma. Chapter 11 - Green synthesis of metallic nanoparticles: a review, Editor(s): R. Praveen Kumar, B. Bharathiraja, Nanomaterials, Academic Press, 2021.

23) Bankier C, Matharu R, Cheong YK. Synergistic antibacterial effects of metallic nanoparticle combinations. Sci Rep 2019; 9: 16074.

24) Shaikh S. Mechanistic insights into the antimicrobial actions of metallic nanoparticles and their implications for multidrug resistance. Int J Mol Sci 2019; 20: 2468.

25) Nisar P, Ali N, Rahman L. Antimicrobial activities of biologically synthesized metal nanoparticles: an insight into the mechanism of action. J Biol Inorg Chem 2019; 24: 929-941.

26) Chatterjee T, Chatterjee BK, Majumdar D, Chakrabarti P. Antibacterial effect of silver nanoparticles and the modeling of bacterial growth kinetics using a modified Gompertz model. Biochim Biophys Acta 2015; 1850: 299-306.

27) Yin JJ, Liu J, Ehrenshaft M. Phototoxicity of nano titanium dioxides in HaCaT keratinocytes - generation of reactive oxygen species and cell damage. Toxicol Appl Pharmacol 2012; 263: 81-88.

28) Slavin YN, Asnis J, Häfeli UO, Bach H. Metal nanoparticles: understanding the mechanisms behind antibacterial activity. J Nanobiotechnology 2017; 15: 65.

29) Gou N, Onnis-Hayden A, Gu AZ. Mechanistic toxicity assessment of nanomaterials by whole-cell-array stress genes expression analysis. Environ Sci Technol 2010; 44: 5964-5970.

30) Gilbert DL, Colton CA. Reactive oxygen species in biological systems: An interdisciplinary approach. Kluwer Academic Publishers, New York, 1999.

31) Butler KS, Peeler DJ, Casey BJ, Dair BJ, Elespuru RK. Silver nanoparticles: correlating nanoparticle size and cellular uptake with genotoxicity. Mutagenesis 2015; 30: 577-591.

32) Chiang HM, Xia Q, Zou X. Nanoscale ZnO induces cytotoxicity and DNA damage in human cell lines and rat primary neuronal cells. J Nanosci Nanotechnol 2012; 12: 2126-2135.

33) Hussain S, Garantziotis S, Rodrigues-Lima F, Dupret JM, Baeza-Squiban A, Boland S. Intracellular signal modulation by nanomaterials. Adv Exp Med Biol 2014; 811: 111-134.

34) Roguska A, Belcarz A, Pisarek M, Ginalska G, Lewandowska M. TiO_2 nanotube composite layers as delivery system for ZnO and Ag nanoparticles - an unexpected overdose effect decreasing their antibacterial efficacy. Mater Sci Eng C Mater Biol Appl 2015; 51: 158-166.

35) Su Y, Zheng X, Chen Y, Li M, Liu K. Alteration of intracellular protein expressions as a key mechanism of the deterioration of bacterial denitrification caused by copper oxide nanoparticles. Sci Rep 2015; 5: 15824.

36) Qiu W, Zheng X, Wei Y. D-alanine metabolism is essential for growth and biofilm formation of Streptococcus mutans. Mol Oral Microbiol 2016; 31: 435-444.

37) Salavati-niasari M, Davar F, Mir N. Synthesis and characterization of metallic copper nanoparticles via thermal decomposition. Polyhedron 2008; 27: 3514-3518.

38) Sathiyaraj S, Suriyakala G, Dhanesh Gandhi A, Babujanarthanam R, Almaary KS, Chen TW, Ka-

viyarasu K. Biosynthesis, characterization, and antibacterial activity of gold nanoparticles. J Infect Public Health 2021; 14: 1842-1847.

39) Das SK, Das AR, Guha AK. Gold Nanoparticles: Microbial Synthesis and Application in Water Hygiene Management. Langmuir 2009; 25: 8192-8199.

40) Gulati S, Singh P, Diwan A, Mongia A, Kumar S. Functionalized gold nanoparticles: promising and efficient diagnostic and therapeutic tools for HIV/AIDS. RSC Med Chem 2020; 11: 1252-1266.

41) Li X, Robinson SM, Gupta A, Saha K, Jiang Z, Moyano DF, Sahar A, Riley MA, Rotello VM. Functional gold nanoparticles as potent antimicrobial agents against multi-drug-resistant bacteria. ACS Nano 2014; 8: 10682-10686.

42) Arafa MG, El-Kased RF, Elmazar MM. Thermoresponsive gels containing goldnanoparticles as smart antibacterial and wound healing agents. Sci Rep 2018; 8: 1-6.

43) Nayem SMA, Sultana N, Haque MA, Miah B, Hasan MM, Islam T, Hasan MM, Awal A, Uddin J, Aziz MA, Ahammad AJS. Green Synthesis of Gold and Silver Nanoparticles by Using Amorphophallus paeoniifolius Tuber Extract and Evaluation of Their Antibacterial Activity. Molecules 2020; 25: 4773.

44) Rajan A, Vilas V, Philip D. Studies on catalytic, antioxidant, antibacterial and anticancer activities of biogenic gold nanoparticles. J Mol Liq 2015; 212: 331-339.

45) Thomas B, Vithiya BSM, Prasad TAA, Mohamed SB, Magdalane CM, Kaviyarasu K, Maaza M. Antioxidant and Photocatalytic Activity of Aqueous Leaf Extract Mediated Green Synthesis of Silver Nanoparticles Using Passiflora edulis f. flavicarpa. J Nanosci Nanotechnol 2019; 19: 2640-2648.

46) Kumar V, Yadav SK. Plant-mediated synthesis of silver and gold nanoparticles and their applications. J Chem Technol Biotechnol 2009; 84: 151-157.

47) MubarakAli D, Thajuddin N, Jeganathan K, Gunasekaran M. Plant extract mediated synthesis of silver and gold nanoparticles and its antibacterial activity against clinically isolated pathogens. Colloids Surf B Biointerfaces 2011; 85: 360-365.

48) Vijayan R, Joseph S, Mathew B. Indigofera tinctoria leaf extract mediated green synthesis of silver and gold nanoparticles and assessment of their anticancer, antimicrobial, antioxidant and catalytic properties. Artif Cells Nanomed Biotechnol 2018; 46: 861-871.

49) Jayaseelan C, Rahuman AA, Kirthi AV, Marimuthu S, Santhoshkumar T, Bagavan A, Gaurav K, Karthik L, Rao KV. Novel microbial route to synthesize ZnO nanoparticles using Aeromonas hydrophila and their activity against pathogenic bacteria and fungi. Spectrochim Acta A Mol Biomol Spectrosc 2012; 90: 78-84.

50) Beyth N, Houri-Haddad Y, Domb A, Khan W, Hazan R. Alternative antimicrobial approach: nano-antimicrobial materials. Evid Based Complement Alternat Med 2015; 2015: 246012.

51) Aparicio-Caamaño M, Carrillo-Morales M, Olivares-Trejo JJ. Iron oxide nanoparticle improves the antibacterial activity of erythromycin. J Bacteriol Parasitol 2016; 7: 267.

52) Armijo LM, Wawrzyniec SJ, Kopciuch M. Antibacterial activity of iron oxide, iron nitride, and tobramycin conjugated nanoparticles against Pseudomonas aeruginosa biofilms. J Nanobiotechnol 2020; 18: 35.

53) Batool F, Iqbal MS, Khan SU, Khan J, Ahmed B, Qadir MI. Biologically synthesized iron nanoparticles (FeNPs) from Phoenix dactylifera have anti-bacterial activities. Sci Rep 2021; 11: 22132.

54) Tong JW. Case reports on the use of antimicrobial (silver impregnated) soft silicone foam dressing on infected diabetic foot ulcers. Int Wound J 2009; 6: 275-284.

55) Kim YT, Kim K, Han JH, Kimmel RM. Antimicrobial Active Packaging for Food. Smart Packag Technol Fast Mov Consum Goods 2008; 76: 99-110.

56) Kampmann Y, De Clerck E, Kohn S, Patchala DK, Langerock R, Kreyenschmidt J. Study on the antimicrobial effect of silver-containing inner liners in refrigerators. J Appl Microbiol 2008; 104: 1808-1814.

57) Bruna T, Maldonado-Bravo F, Jara P, Caro N. Silver Nanoparticles and Their Antibacterial Applications. Int J Mol Sci 2021; 22: 7202.

58) Marambio-Jones C, Hoek EMV. A review of the antibacterial effects of silver nanomaterials and potential implications for human health and the environment. J Nanopart Res 2010; 12: 1531-1551.

59) Tran QH, Nguyen VQ, Le A. Silver nanoparticles: Synthesis, properties, toxicology, applications and perspectives. Adv Nat Sci Nanosci Nanotechnol 2013; 4: 033001.

60) Ge L, Li Q, Wang M, Ouyang J, Li X, Xing MMQ. Nanosilver particles in medical applications: Synthesis, performance, and toxicity. Int J Nanomed 2014; 9: 2399-2407.

61) Cheng G, Dai M, Ahmed S, Hao H, Wang X, Yuan Z. Antimicrobial drugs in fighting against antimicrobial resistance. Front Microbiol 2016; 7: 470.

62) Das B, Dash SK, Mandal D, Ghosh T, Chattopadhyay S, Tripathy S, Roy S. Green synthesized silver nanoparticles destroy multidrug resistant bacteria via reactive oxygen species mediated membrane damage. Arab J Chem 2017; 10: 862-876.

63) Lee JH, Jeong D, Kanmani P. Study on physical and mechanical properties of the biopolymer/silver based active nanocomposite films with antimicrobial activity. Carbohydr Polym 2019; 224: 115159.

64) Betts JW, Hornsey M, La Ragione RM. Novel Antibacterials: Alternatives to Traditional Antibiotics, 1st ed.; Elsevier Ltd.: Amsterdam, The Netherlands, 2018.

65) Natan M, Banin E. From Nano to Micro: Using nanotechnology to combat microorganisms and

their multidrug resistance. FEMS Microbiol Rev 2017; 41: 302-322.

66) Yaqoob AA, Umar K, Ibrahim MNM. Silver nanoparticles: Various methods of synthesis, size affecting factors and their potential applications—A review. Appl Nanosci 2020; 10: 1369-1378.

67) Ahmed MJ, Murtaza G, Rashid F, Iqbal J. Eco-friendly green synthesis of silver nanoparticles and their potential applications as antioxidant and anticancer agents. Drug Dev Ind Pharm 2019; 45: 1682-1694.

68) Belova MM, Shipunova VO, Kotelnikova PA, Babenyshev AV, Rogozhin EA, Cherednichenko MYC, Deyev SM. Green synthesis of cytotoxic silver nanoparticles based on secondary metabolites of Lavandula angustifolia Mill. Acta Naturae 2019; 11: 47-53.

69) Foroohimanjili F, Mirzaie A, Hamdi SMM, Noorbazargan H, Hedayati Ch M, Dolatabadi A, Rezaie H, Bishak FM. Antibacterial, antibiofilm, and anti-quorum sensing activities of phytosynthesized silver nanoparticles fabricated from Mespilus germanica extract against multidrug resistance of Klebsiella pneumoniae clinical strains. J Basic Microbiol 2020; 60: 216-230.

70) Kumar DA, Palanichamy V, Roopan SM. Green synthesis of silver nanoparticles using Alternanthera dentata leaf extract at room temperature and their antimicrobial activity. Spectrochim Acta A Mol Biomol Spectrosc 2014; 127: 168-171.

71) Maiti S, Krishnan D, Barman G, Kumar Gosh S, Konar Laha J. Antimicrobial activities of silver nanoparticles synthesized from Lycopersicon esculentum extract. J Anal Sci Technol 2014; 5: 40.

72) Tai CY, Tai C, Chang M, Liu H. Synthesis of Magnesium Hydroxide and Oxide Nanoparticles Using a Spinning Disk Reactor. Ind Eng Chem Res 2007; 46: 5536-5541.

73) Nithiyavathi R, John Sundaram S, Theophil Anand G, Raj Kumar D, Dhayal Raj A, Al Farraj DA, Aljowaie RM, AbdelGawwad MR, Samson Y, Kaviyarasu K. Gum mediated synthesis and characterization of CuO nanoparticles towards infectious disease-causing antimicrobial resistance microbial pathogens. J Infect Public Health 2021; 14: 1893-1902.

74) Kruk T, Szczepanowicz K, Stefanska J, Socha RP, Warszyński P. Synthesis and antimicrobial activity of monodisperse copper nanoparticles. Colloids Surf B Biointerfaces 2015; 128: 17-22.

75) Prado JV, Vidal AR, Duran TC. Application of copper bactericidal properties in medical practice. Rev Med Chil 2012; 140: 1325-1332.

76) Hans M, Erbe A, Mathews S, Chen Y, Solioz M. Role of copper oxides in contact killing of bacteria. Langmuir 2013; 29: 16160-16166.

77) Thekkae Padil VV, Cerník M. Green synthesis of copper oxide nanoparticles using gum karaya as a biotemplate and their antibacterial application. Int J Nanomed 2013; 8: 889-898.

78) Nene A, Tuli HS. Synergistic effect of copper nanoparticles and antibiotics to enhance antibacterial potential. Biomaterials 2019; 1: 33-47.

79) Lee HJ, Lee G, Jang NR, Yun JH, Song JY, Kim BS. Biological synthesis of copper nanoparticles using plant extract. Nanotechnology 2011; 1: 371-374.

80) Shende S, Ingle AP, Gade A, Rai M. Green synthesis of copper nanoparticles by Citrus medica Linn. (Idilimbu) juice and its antimicrobial activity. World J Microbiol Biotechnol 2015; 31: 865-873.

81) Ren G, Hu D, Cheng EW, Vargas-Reus MA, Reip P, Allaker RP. Characterisation of copper oxide nanoparticles for antimicrobial applications. Int J Antimicrob Agents 2009; 33: 587-590.

82) Celesti C, Gervasi T, Cicero N, Giofrè SV, Espro C, Piperopoulos E, Gabriele B, Mancuso R, Lo Vecchio G, Iannazzo D. Titanium Surface Modification for Implantable Medical Devices with Anti-Bacterial Adhesion Properties. Materials (Basel) 2022; 15: 3283.

83) Khashan KS, Sulaiman GM, Abdulameer FA, Albukhaty S, Ibrahem MA, Al-Muhimeed T, AlObaid, AA. Antibacterial Activity of TiO_2 Nanoparticles Prepared by One-Step Laser Ablation in Liquid. Appl Sci 2021; 11: 4623.

84) Ahmed FY, Aly UF, Abd El-Baky RM, Waly NG-FM. Effect of Titanium Dioxide Nanoparticles on the Expression of Efflux Pump and Quorum-Sensing Genes in MDR Pseudomonas aeruginosa Isolates. Antibiotics (Basel) 2021; 10: 625.

85) Ahmed FY, Farghaly Aly U, Abd El-Baky RM, Waly NGFM. Comparative Study of Antibacterial Effects of Titanium Dioxide Nanoparticles Alone and in Combination with Antibiotics on MDR Pseudomonas aeruginosa Strains. Int J Nanomedicine 2020; 15: 3393-3404.

86) Jayaseelan C, Ramkumar R, Rahuman AA, Perumal P. Green synthesis of gold nanoparticles using seed aqueous extract of Abelmoschus esculentus and its antifungal activity. Ind Crops Prod 2013; 45: 423-429.

87) Xie Y, He Y, Irwin PL, Jin T, Shi X. Antibacterial activity and mechanism of action of zinc oxide nanoparticles against Campylobacter jejuni. Appl Environ Microbiol 2011; 77: 2325-2331.

88) Horky P, Skalickova S, Urbankova L. Zinc phosphate-based nanoparticles as a novel antibacterial agent: In vivo study on rats after dietary exposure. J Animal Sci Biotechnol 2019; 10: 17.

89) Chaudhary P, Fatima F, Kumar A. Relevance of nanomaterials in food packaging and its advanced future prospects. J Inorg Organomet Polym 2020; 30: 1-13.

90) Hayat S, Muzammil S, Rasool MH, Nisar Z, Hussain SZ, Sabri AN, Jamil S. In vitro antibiofilm and anti-adhesion effects of magnesium oxide nanoparticles against antibiotic resistant bacteria. Microbiol Immunol 2018; 62: 211-220.

91) Nguyen NYT, Grelling N, Wetteland CL, Rosario R, Liu H. Antimicrobial Activities and Mechanisms of Magnesium Oxide Nanoparticles (nMgO) against Pathogenic Bacteria, Yeasts, and Biofilms. Sci Rep 2018; 8: 16260.

92) Sakthiraj K, Karthikeyan B. Synthesis and characterization of cerium oxide nanoparticles using different solvents for electrochemical applications. Appl Phys A 2020; 126: 52.

93) Dhall A, Self W. Cerium Oxide Nanoparticles: A Brief Review of Their Synthesis Methods and Biomedical Applications. Antioxidants (Basel) 2018; 7: 97.

94) Kannan SK, Sundrarajan M. A green approach for the synthesis of a cerium oxide nanoparticle: Characterization and antibacterial activity. Int J Nanosci 2014; 13: 1450018.

95) Munusamy S, Bhakyaraj K, Vijayalakshmi L, Stephen A, Narayanan V. Synthesis and characterization of cerium oxide nanoparticles using curvularia lunata and their antibacterial properties. Int J Innov Res Sci Eng 2014; 2: 318-323.

96) Kargar H, Ghazavi H, Darroudi M. Size-controlled and bio-directed synthesis of ceria nanopowders and their in vitro cytotoxicity effects. Ceram Int 2015; 41: 4123-4128.

97) Qi M, Li W, Zheng X, Li X, Sun Y, Wang Y, Li C and Wang L. Cerium and Its Oxidant-Based Nanomaterials for Antibacterial Applications: A State-of-the-Art Review. Front Mater 2020; 7: 213.

98) Falsini B, Bush RA, Sieving PA. Chapter 37 - Neuroprotection, Editor(s): Stephen J. Ryan, SriniVas R. Sadda, David R. Hinton, Andrew P. Schachat, SriniVas R. Sadda, C.P. Wilkinson, Peter Wiedemann, Andrew P. Schachat, Retina (Fifth Edition), W.B. Saunders, 2013.

99) Kalaycıoğlu Z, Kahya N, Adımcılar V, Kaygusuz H, Torlak E, Akın-Evingür G, Erim FB. Antibacterial nano cerium oxide/chitosan/cellulose acetate composite films as potential wound dressing. Eur Polym J 2020; 133: 566-564.

100) Bellio P, Luzi C, Mancini A, Cracchiolo S, Passacantando M, Di Pietro L, Perilli M, Amicosante G, Santucci S, Celenza G. Cerium oxide nanoparticles as potential antibiotic adjuvant. Effects of CeO_2 nanoparticles on bacterial outer membrane permeability. Biochim Biophys Acta Biomembr 2018; 1860: 2428-2435.

101) Marquis RE. Antimicrobial actions of fluoride for oral bacteria. Can J Microbiol 1995; 41: 955-964.

102) Marquis RE, Clock SA, Mota-Meira M. Fluoride and organic weak acids as modulators of microbial physiology. FEMS Microbiol Rev 2003; 26: 493-510.

103) Lellouche J, Friedman A, Gedanken A, Banin E. Antibacterial and antibiofilm properties of yttrium fluoride nanoparticles. Int J Nanomedicine 2012; 7: 5611-5624.

104) Fang FC. Antimicrobial reactive oxygen and nitrogen species: concepts and controversies. Nat Rev Microbiol 2004; 2: 820-832.

105) Raulli R, McElhaney-Feser G, Hrabie JA, Cihlar RL. Antimicrobial properties of nitric oxide using diazeniumdiolates as the nitric oxide donor. Rec Res Devel Microbiol 2002; 6: 177-183.

106) Ghaffari A, Miller CC, McMullin B, Ghahary A. Potential application of gaseous nitric oxide as a topical antimicrobial agent. Nitric Oxide 2006; 14: 21-29.

107) Hetrick EM, Shin JH, Stasko NA, Johnson CB, Wespe DA, Holmuhamedov E, Schoenfisch MH. Bactericidal efficacy of nitric oxide-releasing silica nanoparticles. ACS Nano 2008; 2: 235-246.

108) Hetrick EM, Shin JH, Paul HS, Schoenfisch MH. Anti-biofilm efficacy of nitric oxide-releasing silica nanoparticles. Biomaterials 2009; 30: 2782-2789.

109) Rawat M, Singh D, Saraf S, Saraf S. Development and in vitro evaluation of alginate gel-encapsulated, chitosan-coated ceramic nanocores for oral delivery of enzyme. Drug Dev Ind Pharm 2008; 34: 181-188.

110) Thomas S, Kumar Mishra P, Talegaonkar S. Ceramic nanoparticles: fabrication methods and applications in drug delivery. Curr Pharm Des 2015; 21: 6165-6188.

111) Khan I, Saeed K, Khan I. Nanoparticles: properties, applications and toxicities. Arab J Chem 2019; 12: 908-931.

112) Moreno-Vega AI, Gomez-Quintero T, Nunez-Anita R-E, Acosta-Torres L-S, Castaño V. Polymeric and ceramic nanoparticles in biomedical applications. J Nanotechnol 2012; 32: 126-147.

113) Singh D, Dubey P, Pradhan M, Rawat M. Ceramic nanocarriers: versatile nanosystem for protein and peptide delivery. Expert Opin Drug Deliv 2013; 10: 241-259.

114) Ciobanu CS, Iconaru SL, Popa CL, Motelica-Heino M, Predoi D. Evaluation of Samarium Doped Hydroxyapatite, Ceramics for Medical Application: Antimicrobial Activity. J Nanomater 2015; 2015: 11.

115) Iconaru SL, Groza A, Gaiaschi S, Rokosz K, Raaen S, Ciobanu SC, Chapon P, Predoi D. Antimicrobial Properties of Samarium Doped Hydroxyapatite Suspensions and Coatings. Coatings 2020; 10: 1124.

116) Malarkodi CS, Rajeshkumar K, Paulkumar M, Vanaja G, Gnanajobitha G, Annadurai. Biosynthesis and Antimicrobial Activity of Semiconductor Nanoparticles against Oral Pathogens. Bioinorg Chem Appl 2014; 2014: 347167.

117) Lyon DY, Brunet L, Hinkal GW, Wiesner MR, Alvarez PJ. Antibacterial activity of fullerene water suspensions (nC60) is not due to ROS-mediated damage. Nano Lett 2008; 8: 1539-1543.

118) Iravani S, Korbekandi H, Mirmohammadi SV, Zolfaghari B. Synthesis of silver nanoparticles: chemical, physical and biological methods. Res Pharm Sci 2014; 9: 385-406.

119) Long CM, Nascarella MA, Valberg PA. Carbon black vs black carbon and other airborne materials containing elemental carbon: physical and chemical distinctions. Environ Pollut 2013; 181: 271-286.

120) Shvedova AA, Pietroiusti A, Fadeel B, Kagan VE. Mechanisms of carbon nanotube-induced toxicity: focus on oxidative stress. Toxicol Appl Pharmacol 2012; 261: 121-133.

121) Cataldo F, Da Ros T. Medicinal chemistry and pharmacological potential of fullerenes and carbon nanotubes. Trieste: Springer 2008.

122) Tegos GP, Demidova TN, Arcila-Lopez D, Lee H, Wharton T, Gali H. Hamblin MR. Cationic fullerenes are effective and selective antimicrobial photosensitizers. Chem Biol 2005; 12: 1127-1135.

123) Zhang X, Cong H, Yu B, Chen Q. Recent advances of water-soluble fullerene derivatives in biomedical applications. Mini-Rev Org Chem 2019; 16: 92-99.

124) Díez-Pascual AM. State of the Art in the Antibacterial and Antiviral Applications of Carbon-Based Polymeric Nanocomposites. Int J Mol Sci 2021; 22: 10511.

125) Alekseeva O, Bagrovskaya N, Noskov A. Polystyrene film composites filled with fullerenes. In Proceedings of the International Conference Nanomaterials: Applications and Properties, Alusha, Ukranie, 2013.

126) Hui L, Piao J, Auletta J, Hu K, Zhu Y, Meyer T, Liu H, Yang L. Availability of the Basal Planes of Graphene Oxide Determines Whether It Is Antibacterial. ACS Appl Mater Interfaces 2014; 6: 13183-13190.

127) Maleki Dizaj S, Mennati A, Jafari S, Khezri K, Adibkia K. Antimicrobial activity of carbon-based nanoparticles. Adv Pharm Bull 2015; 5: 19-23.

128) Azimi S, Behin J, Abiri R, Rajabi L, Derakhshan AA, Karimnezhad H. Synthesis, Characterization and Antibacterial Activity of Chlorophyllin Functionalized Graphene Oxide Nanostructures. Sci Adv Mater 2014; 6: 771-781.

129) Mohammed H, Kumar A, Bekyarova E, Al-Hadeethi Y, Zhang X, Chen M, Ansari MS, Cochis A, Rimondini L. Antimicrobial Mechanisms and Effectiveness of Graphene and Graphene-Functionalized Biomaterials. A Scope Review. Front Bioeng Biotechnol 2020; 8: 465.

130) Bacali C, Baldea I, Moldovan M, Carpa R, Olteanu DE, Filip GA, Nastase V, Lascu L, Badea M, Constantiniuc M, Badea F. Flexural strength, biocompatibility, and antimicrobial activity of a polymethyl methacrylate denture resin enhanced with graphene and silver nanoparticles. Clin Oral Investig 2020; 24: 2713-2725.

131) Gomez-Gualdrón DA, Burgos JC, Yu J, Balbuena PB. Carbon nanotubes: engineering biomedical applications. Prog Mol Biol Transl Sci 2011; 104: 175-245.

132) Visalli G, Bertuccio MP, Iannazzo D, Piperno A, Pistone A, Di Pietro A. Toxicological assessment of multi-walled carbon nanotubes on A549 human lung epithelial cells. Toxicol In Vitro 2015; 29: 352-362.

133) Visalli G, Currò M, Iannazzo D, Pistone A, Pruiti Ciarello M, Acri G, Testagrossa B, Bertuccio MP, Squeri R, Di Pietro A. In vitro assessment of neurotoxicity and neuroinflammation of homemade MWCNTs. Environ Toxicol Pharmacol 2017; 56: 121-128.

134) Visalli G, Facciolà A, Iannazzo D, Piperno A, Pistone A, Di Pietro A. The role of the iron catalyst in the toxicity of multi-walled carbon nanotubes (MWCNTs). J Trace Elem Med Biol 2017; 43: 153-160.

135) Visalli G, Facciolà A, Currò M, Laganà P, La Fauci V, Iannazzo D, Pistone A, Di Pietro A. Mitochondrial Impairment Induced by Sub-Chronic Exposure to Multi-Walled Carbon Nanotubes. Int J Environ Res Public Health 2019; 16: 792.

136) Trovato MC, Andronico D, Sciacchitano S, Ruggeri RM, Picerno I, Di Pietro A, Visalli G. Nanostructures: between natural environment and medical practice. Rev Environ Health 2018; 33: 295-307.

137) Facciolà A, Visalli G, La Maestra S, Ceccarelli M, D'Aleo F, Nunnari G, Pellicanò GF, Di Pietro A. Carbon nanotubes and central nervous system: Environmental risks, toxicological aspects and future perspectives. Environ Toxicol Pharmacol 2019; 65: 23-30.

138) Al-Jumaili A, Alancherry S, Bazaka K, Jacob MV. Review on the Antimicrobial Properties of Carbon Nanostructures. Materials (Basel) 2017; 10: 1066.

139) Kang S, Herzberg M, Rodrigues DF, Elimelech M. Antibacterial effects of carbon nanotubes: size does matter! Langmuir 2008; 24: 6409-6413.

140) Smith SC, Rodrigues DF. Carbon-based nanomaterials for removal of chemical and biological contaminants from water: A review of mechanisms and applications. Carbon 2015; 91: 122-143.

141) Yang C, Mamouni J, Tang Y, Yang L. Antimicrobial activity of single-walled carbon nanotubes: Length effect. Langmuir 2010; 26: 16013-16019.

142) Arias LR, Yang L. Inactivation of bacterial pathogens by carbon nanotubes in suspensions. Langmuir 2009; 25: 3003-3012.

143) Laganà P, Visalli G, Facciolà A, Ciarello MP, Laganà A, Iannazzo D, Di Pietro A. Is the Antibacterial Activity of Multi-Walled Carbon Nanotubes (MWCNTs) Related to Antibiotic Resistance? An Assessment in Clinical Isolates. Int J Environ Res Public Health 2021; 18: 9310.

144) Yuan W, Jiang G, Che J, Qi X, Xu R, Chang MW. Deposition of silver nanoparticles on multiwalled carbon nanotubes grafted with hyperbranched poly (amidoamine) and their antimicrobial effects. J Phys Chem C 2008; 112: 18754-18759.

145) Seo Y, Hwang J, Kim J, Jeong Y, Hwang M, Choi J. Antibacterial activity and cytotoxicity of multi-walled carbon nanotubes decorated with silver nanoparticles. Int J Nanomed 2014; 9: 4621-4629.

146) Morsi RE, Alsabagh AM, Nasr SA, Zaki MM. Multifunctional nanocomposites of chitosan, silver nanoparticles, copper nanoparticles and carbon nanotubes for water treatment: Antimicrobial characteristics. Int J Biol Macromol 2017; 97: 264-269.

147) Ahmed F, Santos CM, Vergara RAMV, Tria MCR, Advincula R, Rodrigues DF. Antimicrobial applications of electroactive PVK-SWNT nanocomposites. Environ Sci Technol 2012; 46: 1804-1810.

148) Pan K, Zhong Q. Organic nanoparticles in foods: fabrication, characterization, and utilization. Annu Rev Food Sci Technol 2016; 7: 245-266.

149) Gujrati M, Malamas A, Shin T, Jin E, Sun Y, Lu ZR. Multifunctional cationic lipid-based nanoparticles facilitate endosomal escape and reduction-triggered cytosolic siRNA release. Mol Pharm 2014; 11: 2734-2744.

150) Facciolà A, Visalli G, Laganà P, La Fauci V, Squeri R, Pellicanò GF, Nunnari G, Trovato M, Di Pietro A. The new era of vaccines: the "nanovaccinology". Eur Rev Med Pharmacol Sci 2019; 23: 7163-7182.

151) Ali A, Ahmed S. A review on chitosan and its nanocomposites in drug delivery. Int J Biol Macromol 2018; 109: 273-286.

152) No HK, Park NY, Lee SH, Meyers SP. Antibacterial activity of chitosans and chitosan oligomers with different molecular weights. Int J Food Microbiol 2002; 74: 65-72.

153) Jeihanipour A, Karimi K, Taherzadeh MJ. Antimicrobial properties offungal chitosan, research. J Biol Sci 2007; 2: 239-243.

154) Yilmaz Atay H. Antibacterial Activity of Chitosan-Based Systems. Functional Chitosan 2020; 23: 457-489.

155) Divya K, Vijayan S, Tijith KG, Jisha MS. Antimicrobial properties of chitosan nanoparticles: mode of action and factors affecting activity. Fibers Polym 2017; 18: 221-230.

156) Legnani L, Iannazzo D, Pistone A, Celesti C, Giofrè S, Romeo R, Di Pietro A, Visalli G, Fresta M, Bottino P, Blanco I, Chiacchio MA. Functionalized polyhedral oligosilsesquioxane (POSS) based composites for bone tissue engineering: synthesis, computational and biological studies. RSC Adv 2020; 10: 11325-11334.

157) Zaki NM, Hafez MM. Enhanced antibacterial effect of ceftriaxone sodiumloaded chitosan nanoparticles against intracellular Salmonella typhimurium. AAPS PharmSciTech 2012; 13: 411-421.

158) Jamil B, Habib H, Abbasi S, Nasir H, Rahman A, Rehman A, Bokhari H, Imran M. Cefazolin loaded chitosan nanoparticles to cure multi drug resistant Gram-negative pathogens. Carbohydr Polym 2016; 136: 682-691.

159) Sadeghi AMM, Dorkoosh FA, Avadi MR, Saadat P, Rafiee-Tehrani M, Junginger HE. Preparation, characterization and antibacterial activities of chitosan, N-trimethyl chitosan (TMC) and N-diethylmethyl chitosan (DEMC) nanoparticles loaded with insulin using both the ionotropic gelation and polyelectrolyte complexation methods. Int J Pharm 2008; 355: 299-306.

160) Kong M, Chen XG, Xing K, Park HJ. Antimicrobial properties of chitosan and mode of action: a state of the art review. Int J Food Microbiol 2010; 144: 51-63.

161) Bhattacharjee S, Joshi R, Yasir M, Adhikari A, Chughtai AA, Heslop D, Bull R, Willcox M, Macintyre CR. Graphene- and Nanoparticle-Embedded Antimicrobial and Biocompatible Cotton/Silk Fabrics for Protective Clothing. ACS Appl Bio Mater 2021; 4: 6175-6185.

162) Hiragond CB, Kshirsagar AS, Dhapte VV, Khanna T, Joshi P, More PV. Enhanced anti-microbial response of commercial face mask using colloidal silver nanoparticles. Vacuum 2018; 156: 475-482.

163) Kalita S, Kandimalla R, Bhowal AC. Kotoky J, Kundu S. Functionalization of β-lactam antibiotic on lysozyme capped gold nanoclusters retrogress MRSA and its persisters following awakening. Sci Rep 2018; 8: 5778.

164) Konop M, Czuwara J, Kłodzińska E, Laskowska AK, Sulejczak D, Damps T, Zielenkiewicz U, Brzozowska I, Sureda A, Kowalkowski T, Schwartz RA, Rudnicka L. Evaluation of keratin biomaterial containing silver nanoparticles as a potential wound dressing in full-thickness skin wound model in diabetic mice. J Tissue Eng Regen Med 2020; 14: 334-346.

165) Gupta A, Briffa SM, Swingler S, Gibson H, Kannappan V, Adamus G, Kowalczuk M, Martin C, Radecka I. Synthesis of Silver Nanoparticles Using Curcumin-Cyclodextrins Loaded into Bacterial Cellulose-Based Hydrogels for Wound Dressing Applications. Biomacromolecules 2020; 21: 1802-1811.

166) Li XX, Dong JY, Li YH, Zhong J, Yu H, Yu QQ, Lei M. Fabrication of Ag-ZnO@ carboxymethyl cellulose/K-carrageenan/graphene oxide/konjac glucomannan hydrogel for effective wound dressing in nursing care for diabetic foot ulcers. Appl Nanosci 2020; 10: 729-738.

167) Sun CY, Che YJ, Lu SJ. Preparation and application of collagen scaffold-encapsulated silver nanoparticles and bone morphogenetic protein 2 for enhancing the repair of infected bone. Biotechnol Lett 2015; 37: 467-473

168) Dalavi PA, Prabhu A, Shastry RP, Venkatesan J. Microspheres containing biosynthesized silver nanoparticles with alginate-nano hydroxyapatite for biomedical applications. J Biomater Sci Polym Ed 2020; 31: 2025-2043.

169) Alpaslan E, Geilich BM, Yazici H, Webster TJ. pH-Controlled Cerium Oxide Nanoparticle Inhibition of Both Gram-Positive and Gram-Negative Bacteria Growth. Sci Rep 2017; 7: 1-12.

170) Angelina JTT, Ganesan S, Panicker TMR, Narayani R, Paul Korath M, Jagadeesan K. Pulsed laser deposition of silver nanoparticles on prosthetic heart valve material to prevent bacterial infection. Mater Technol 2017; 32: 148-155.

171) Kuo J, Tan S, Hsiao Y, Mutalik C, Chen H, Yougbare S, Kuo T. Unveiling the Antibacterial Mechanism of Gold Nanoclusters via In Situ Transmission Electron Microscopy. ACS Sustain Chem Eng 2022; 10: 464-471.

172) Lishchynskyi O, Shymborska Y, Stetsyshyn Y, Raczkowska J, Skirtach A, Peretiatko T, Budkowski A. Passive antifouling and active self-dis-

infecting antiviral surfaces. Chem Eng J 2022; 446: 137048.

173) Bao X, Huang X, Jin X, Hu Q. Bactericidal Anti-Adhesion Potential Integrated Polyoxazoline/Silver Nanoparticle Composite Multilayer Film with pH Responsiveness. Polymers (Basel) 2022; 14: 3685.

174) Lundin PM, Fiser BL, Blackledge MS, Pickett HL, Copeland AL. Functionalized Self-Assembled Monolayers: Versatile Strategies to Combat Bacterial Biofilm Formation. Pharmaceutics 2022; 14: 1613.

175) Yliniemi K, Vahvaselkä M, Ingelgem YV, Baert K, Wilson BP, Terryn H, Kontturi K. The formation and characterisation of ultra-thin films containing Ag nanoparticles. J Mater Chem 2008; 18: 199-206.

176) Juan L, Zhimin Z, Anchun M, Lei L, Jingchao Z. Deposition of silver nanoparticles on titanium surface for antibacterial effect. Int J Nanomed 2010; 5: 261-267.

177) Pallavicini P, Taglietti A, Dacarro, G, Diaz-Fernandez YA, Galli M, Grisoli P, Patrini M, Santucci De Magistris G, Zanoni R. Self-assembled monolayers of silver nanoparticles firmly grafted on glass surfaces: Low Ag^{+} release for an efficient antibacterial activity. J Colloid Interface Sci 2010; 350: 110-116.

178) Pallavicini P, Dacarro G, Cucca L, Denat F, Grisoli P, Patrini M, Sok N, Taglietti A. A monolayer of a Cu^{2+}-tetraazamacrocyclic complex on glass as the adhesive layer for silver nanoparticles grafting, in the preparation of surface-active antibacterial materials. New J Chem 2011; 35: 1198-1201.

179) Taglietti A, Arciola CR, D'Agostino A, Dacarro G, Montanaro L, Campoccia D, Cucca L, Vercellino M, Poggi A, Pallavicini P, Visai L. Antibiofilm activity of a monolayer of silver nanoparticles anchored to an amino-silanized glass surface. Biomaterials 2014; 35: 1779-1788.

180) Gargioni C, Borzenkov M, D'Alfonso L, Sperandeo P, Polissi A, Cucca L, Dacarro G, Grisoli P, Pallavicini P, D'Agostino A, Taglietti A. Self-Assembled Monolayers of Copper Sulfide Nanoparticles on Glass as Antibacterial Coatings. Nanomaterials 2020; 10: 352.

181) Pajkos A, Deva AK, Vickery K, Cope C, Chang L, Cossart YE. Detection of subclinical infection in significant breast implant capsules. Plast Reconstr Surg 2003; 111: 1605-1611.

182) Schreml S, Heine N, Eisenmann-Klein M, Prantl L. Bacterial colonization is of major relevance for high-grade capsular contracture after augmentation mammaplasty. Ann Plast Surg 2007; 59: 126-130.

183) Virden CP, Dobke MK, Paul S, Lowell Parsons C, Frank DH. Subclinical Infection of the Silicone Breast Implant Surface as a Possible Cause of Capsular Contracture. Aesthetic Plast Surg 2020; 44: 1141-1147.

184) Gominet M, Compain F, Beloin C, Lebeaux D. Central venous catheters and biofilms: Where do we stand in 2017? APMIS 2017; 125: 365-375.

185) Gheorghe DC, Ilie A, Niculescu AG, Grumezescu AM. Preventing Biofilm Formation and Development on Ear, Nose and Throat Medical Devices. Biomedicines 2021; 9: 1025.

186) Gibbs K, Holzman IR. Endotracheal tube: Friend or foe? Bacteria, the endotracheal tube, and the impact of colonization and infection. Semin Perinatol 2012; 36: 454-461.

187) Fernandez-Barat L, Torres A. Biofilms in ventilator-associated pneumonia. Future Microbiol 2016; 11: 1599-1610.

188) Parker LA, Magalhaes M, Desorcy-Scherer K, Torrez Lamberti M, Lorca GL, Neu J. Neonatal Feeding Tube Colonization and the Potential Effect on Infant Health: A Review. Front Nutr 2022; 9: 775014.

189) Akgun D, Perka C, Trampuz A, Renz N. Outcome of hip and knee periprosthetic joint infections caused by pathogens resistant to biofilm-active antibiotics: Results from a prospective cohort study. Arch Orthop Trauma Surg 2018; 138: 635-642.

190) Caldara M, Belgiovine C, Secchi E, Rusconi R. Environmental, Microbiological, and Immunological Features of Bacterial Biofilms Associated with Implanted Medical Devices. Clin Microbiol Rev 2022; 35: e0022120.

191) Khoddami S, Chew BH, Lange D. Problems and solutions of stent biofilm and encrustations: A review of literature. Turk J Urol 2020; 46: S11-S18.

192) Cortese YJ, Wagner VE, Tierney M, Devine D, Fogarty A. Review of Catheter-Associated Urinary Tract Infections and In Vitro Urinary Tract Models. J Health Eng 2018; 2018: 2986742.

193) Khan I, Saeed K, Khan I. Nanoparticles: Properties, applications and toxicities. Arab J Chem 2019; 12, 908-931.