

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 HAI¹. 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 antibiotics³. 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 HAIs⁶⁻⁹. 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 patients¹⁰⁻¹².

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 pathways¹³⁻¹⁵. The CDC reported¹⁶ that in 2019 in the USA, 2.8 million people were infected with antibiotic-resistant bacteria or fungi, and more than

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 attention¹⁷. 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 effect¹⁸.

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 layers²⁰. On the other hand, nanomaterials refer to materials in which at least one of their dimensions is less than 100 nm²¹. As shown in Figure 1, Joudeh and Linke¹⁹ 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 method²⁰. 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 years²². 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 cell¹⁷. 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 studies²⁵ 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

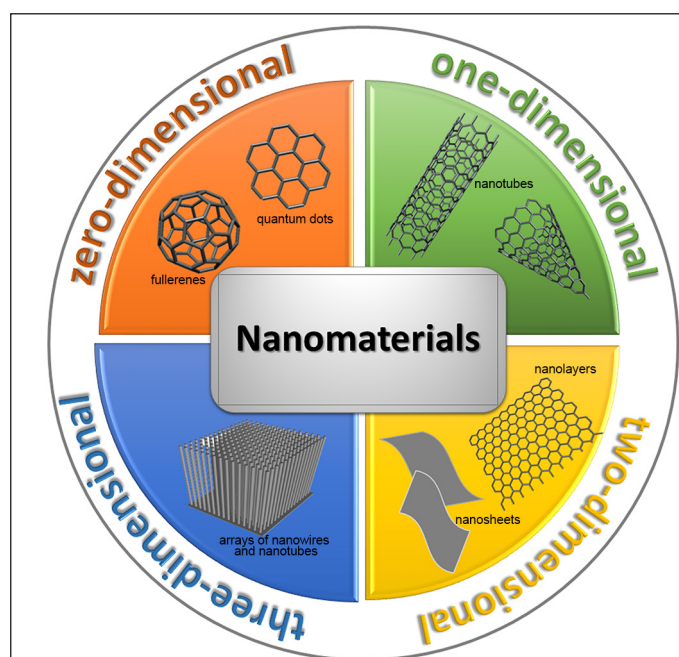


Figure 1. Classification of nanomaterials based on how many dimensions are on nanoscale.

membrane integrity and permeability, generate protein radicals²⁹, promote lipid peroxidation³⁰ and DNA strand breaks and modify nucleic acids³¹. In addition, gene expression can be modulated *via* activation of redox-sensitive transcription factors³², and inflammation can occur through signal transduction³³.

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 (TiO₂NPs) affect the synthesis of adhesion proteins, which are required for biofilm formation³⁶.

Classification of Nanoparticles

NPs are classified according to their constituents into three categories: inorganic, carbon-based and organic²⁰. 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 metal³⁷, 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 target³⁸. 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 content⁴¹. Furthermore, some studies⁴² 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 shown²⁵ 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 synthesis⁴³. Green AuNP synthesis is also preferred because the NPs obtained by this method show higher antibacterial activity compared with those produced by chemical synthesis methods⁴⁴. For example, Nayem et al⁴³ 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 al⁴⁷ biosynthesized AuNPs starting from plant extracts of *Mentha piperita* leaves, with strong bactericidal activity against *Escherichia coli* and *S. aureus*. Vijayan et al⁴⁸ 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 al³⁸ 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 properties³. Beyth et al⁵⁰ 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 al⁵¹, 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 coatings⁵². In recent years, there have been published papers in which the authors discuss green synthesis of these NPs. For example, Batool et al⁵³ 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 industries⁵⁴⁻⁵⁶. 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 form⁵⁷. AgNPs have shown⁵⁸ 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 bacteria⁶¹. 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, <i>E. coli</i> , <i>Pseudomonas spp.</i> , <i>K. pneumoniae</i> , <i>Bacillus subtilis</i> <i>Aspergillus niger</i> , <i>Aspergillus fumigatus</i>	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	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>E. coli</i>	ROS production and oxidative stress.
Silver (Ag) NPs	5-50 nm; spherical	<i>P. aeruginosa</i> , <i>V. cholerae</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> , <i>E. faecium</i> , <i>S. epidermidis</i>	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	<i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i>	Reduction of the cell wall. Alteration of biochemical processes.
Titanium oxide (TiO ₂)	17 nm; hollow nanospheres	<i>E. coli</i> , <i>S. aureus</i> , <i>several fungi</i>	ROS production and DNA damage.
Iron oxide (Fe ₂ O ₃)	10-20 nm; spherical	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>E. coli</i>	ROS production and oxidative stress.
Zinc oxide (ZnO)	28 nm; wurtzite shape	<i>E. coli</i> , <i>Listeria monocytogenes</i> , <i>Salmonella</i> , <i>S. aureus</i>	ROS production with cellular damage for oxidative stress.
Magnesium oxide (MgO) NPs	27 nm; spherical	<i>S. aureus</i> , <i>E. coli</i> , <i>Bacillus megaterium</i> , <i>Bacillus subtilis</i>	ROS production with lipid peroxidation, alkalizing effect.
Cerium oxide (CeO)	Spherical-shaped, nanocubs, nanosheets	<i>E. coli</i> , <i>S. aureus</i> , <i>K. pneumoniae</i>	Altered functionality of plasmatic membrane, ROS production, alteration of the electronic flow and of the transport of nutrients
Other NPs			
Yttrium fluoride (YF)	Needle-like (length of 342 ± 51 nm and a width of 52 ± 12 nm)	<i>E. coli</i> , <i>S. aureus</i>	Binding and inhibition of enzymes containing metal functional groups
NO-releasing silica	Spherical-shaped, 136 ± 15 nm	<i>P. aeruginosa</i> , <i>E. coli</i> , <i>S. aureus</i> , <i>S. epidermidis</i>	ROS production
Ceramic NPs	Amorphous, porous, or polycrystalline	<i>P. aeruginosa</i> , <i>E. coli</i> , <i>E. faecalis</i> , <i>S. aureus</i>	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)	<i>Streptococcus spp.</i> , <i>Staphylococcus spp.</i> , <i>Lactobacillus spp.</i> , <i>K. pneumoniae</i>	Discharge of ions, which react with the thiol groups of the proteins present on the bacterial cell membrane
Carbon-based NPs			
Graphene	Honeycomb lattice	<i>E. coli</i> , <i>S. aureus</i> , <i>S. mutans</i>	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)	<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i>	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)	<i>E. coli</i> , <i>B. subtilis</i>	Interaction with the bacterial surface; ROS production and oxidation of membrane components
Organic NPs			
Chitosan	Linear polycationic heteropolysaccharide	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>S. aureus</i>	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 death⁶². Furthermore, Ag ions can

bind various biomolecules and membranes, altering the integrity of the latter⁶³.

AgNPs, along with other nanomaterials, have been studied⁶⁴ 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 infections⁶⁵. They can also be conjugated to antibiotics, often showing a synergistic effect⁵⁷. In the last 15 years, more than 500 tons of AgNPs have been produced each year⁶⁶. Alongside the classical chemical synthesis of AgNPs, there has been recent attention regarding synthesizing AgNPs through biological approaches such as green synthesis or photosynthesis⁶⁷. 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 used⁶⁸. For example, Foroohimanjili et al⁶⁹ showed how it is possible to photosynthesize 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 al⁷⁰ 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 study⁷¹ 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 reactive⁷². CuO, TiO₂, iron oxide (Fe₂O₃), 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 bacteria⁷³. For this reason, it is used as an antibacterial coating on various substrates, especially medical equipment. Considering that CuSO₄ and Cu(OH)₂, aqueous solutions of Cu, complex copper species

or copper-containing polymers act as antibacterial compounds⁷⁴. 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, leading to DNA degradation and eventual death⁷⁷. A synergistic effect between CuNPs and antibiotics, such as erythromycin, azithromycin and norfloxacin, has also been documented⁷⁸. CuONPs have proved¹⁷ 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 al⁷³ 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 CuSO₄·5H₂O solution as a reducing agent, and these showed⁷⁹ excellent antibacterial potential. *Citrus medica* Linn extract has also been used⁸⁰ 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 al⁸¹ 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 colonisation⁸². However, TiO₂NPs 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 al⁸³ showed an inhibitory effect in *P. aeruginosa*, *A. baumannii*, *K. pneumoniae*, *E. coli* and *S. typhi*. Numerous studies⁸⁴ have also showed the ability

of TiO₂NPs, 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 bio-film production), and with a resistance mechanism, such as efflux pumps. TiO₂NPs are also capable of potentiating the effect of antibiotics. Ahmed et al⁸⁵ reported a reduction in antimicrobial resistance in MDR strains when treated with TiO₂NPs and antibiotics. This is probably due to a synergistic effect. For this reason, TiO₂NPs 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 devices¹⁷.

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 safety⁸⁶. 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 al⁸⁷ 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 death¹⁷. Their antibacterial efficacy has been studied⁸⁸ 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 product⁸⁹.

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 al⁹¹ 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 membrane⁹¹. Hayat et al⁹⁰ 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: Ce³⁺ and Ce⁴⁺ (more stable). This makes it possible to form two different oxides, namely cerium dioxide (CeO₂) and cerium sesquioxide (Ce₂O₃). 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 solvents⁹², but it can also happen with other methods. Dhall and Self⁹³ listed other synthesis methods such as solution precipitation, hydrothermal, solvo-thermal, ball milling, thermal decomposition, spray pyrolysis and thermal hydrolysis. In the same study⁹³, the authors discussed possible synthesis mediated by green plants, fungi and some nutrients. Kannan and Sundrarajan⁹⁴ 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 al⁹⁵ used mycosynthesis with *Curvularia lunata* to make smaller CeONPs. Kargar et al⁹⁶ 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 properties⁹⁷. For these reasons, they are also considered inorganic antioxidants with catalytic activity similar to that of superoxide dismutase (SOD) and catalase⁹⁸, due

to the self-regeneration of their surface based on redox cycling between Ce^{3+} and Ce^{4+} , in response to their surrounding environment⁹³. According to Qi et al⁹⁷, 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 al⁹⁹ 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 glycolysis¹⁰². Lellouche et al¹⁰³ 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 NO¹⁰⁴ produced by immune cells during inflammatory processes and acting as a reactive free radical. Raulli et al¹⁰⁵ demonstrated the efficacy of these NPs on both gram-positive and gram-negative bacteria, while Ghaffari et al¹⁰⁶ showed the same effect on MRSA. Hetrich et al¹⁰⁷ reported that NO-releasing silica NPs showed a bactericidal effect on *P. aeruginosa*. In addition to the bactericidal effect, other studies¹⁰⁸ 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 polycrystalline¹¹¹. They are mainly used in the biomedical field thanks to their high stability and load capacity¹¹². 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 temperature¹¹³. Ciobanu et al¹¹⁴ 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 al¹¹⁵ 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 materials¹¹¹. For example, Malarkodi et al¹¹⁶ 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 carbon²⁰. In addition to causing mechanical da-

mage, carbon nanostructures appear to be able to promote strong ROS generation¹¹⁷. The collective damage is presumably the cause of the antibacterial effect exhibited by carbon-based NPs¹¹⁸. Carbon-based NPs can be classified into fullerenes, graphene, carbon nanotubes (CNTs), carbon nanofibers and carbon black²⁰.

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 structure¹¹⁹. Fullerenes exert antimicrobial activity *via* two modalities: inhibition of energy metabolism following their internalisation¹²⁰ and induction of cell membrane rupture¹²¹. 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 permeation¹²³.

Some studies¹²⁴ have shown how it is possible to combine the activity of fullerenes with that of some nanocompounds. For example, Alekseeva et al¹²⁵ 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 transfer¹²⁶. The bacteriostatic activity of graphene, whether oxidized or not, has been demonstrated¹²⁷ against *E. coli*, and this is probably due to the direct contact between this material and the plasma membrane¹²⁸. 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 water¹²⁹. 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 al¹³⁰, 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 wall¹³¹. 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 studied¹³²⁻¹³⁷. 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 groups¹³⁸. Demonstrating the importance of CNT size, Kang et al¹³⁹ 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 effect¹⁴⁰. 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-efficacy¹⁴¹. Furthermore, due to their nature, they seem to have greater efficacy on spherical-shaped bacteria compared with rod-shaped

bacteria¹³⁸. In addition, functionalized SWCNTs with -OH, -COOH and other surface groups exhibit better antimicrobial activity against both gram-positive and gram-negative bacteria¹⁴², inducing wall damage and releasing the DNA content. In a previous study¹⁴³, 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 effect¹⁴⁴⁻¹⁴⁶. SWCNTs also show¹³⁸ 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 polymers¹⁴⁸. Some examples are dendrimers, protein complexes (ferritin), micelles and liposomes. These NPs are biodegradable, non-toxic and sensitive to heat and electromagnetic radiation¹⁹. 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 chitin¹⁵¹ which occurs naturally in the shells of crustaceans, such as crabs, shrimps and lobsters¹⁵². Recently, some studies¹⁵³ 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. Furthermo-

re, binding to bacterial DNA is possible, causing inhibition of DNA replication and, subsequently, cell death¹⁵⁴. 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 growth¹⁵⁵. 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 engineering¹⁵⁶. Much research¹⁵⁴ 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 antibiotics¹⁵⁷. In some cases, these chitosan NPs also enhance the action of the antibiotic itself. Jamil et al¹⁵⁸ 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 al¹⁵⁹, the effects of chitosan NPs on *S. aureus*, compared with the free soluble polymer, were minor. On the other hand, Kong et al¹⁶⁰ 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 al¹⁶¹ 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 al¹⁶² 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 al¹⁶³ 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 al¹⁶⁴ 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* tests¹⁶⁶.

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 used¹⁶⁷. 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 al¹⁶⁸ 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/CeO₂ NPs which have shown¹⁶⁹, 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 showed¹⁷⁰ 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 cells¹⁷³. SAMs are monolayers (1-5 nm) that can prevent bacterial adhesion by increasing surface hydration or can prevent biofilm formation by disrupting quorum sensing¹⁷⁴. SAMs can be loaded with a wide range of molecules, including NPs. There are many studies¹⁷⁵⁻¹⁸⁰ 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 implants¹⁸¹⁻¹⁸³, central venous catheters¹⁸⁴, cochlear implants¹⁸⁵, endotracheal tube^{186,187}, feeding tube¹⁸⁸, orthopedic implants^{189,190}, stents¹⁹¹ and urinary catheters¹⁹². Multilayers can also be loaded with AgNPs. For example, Bao et al¹⁷³ 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 fields¹⁹³. 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.

Funding

This research received no external funding.

Ethics Approval

Not applicable.

Informed Consent

Not applicable.

Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available within the article.

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Conceptualization: AF and ADP. Methodology: AF, AL and GV. Formal analysis, data curation and writing - original draft: AF and AL. Resources: FC and MF. All Authors revised the manuscript and gave their contribution to improve the paper. All authors read and approved the final manuscript.

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