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A Review on Antibacterial Activity of Nanoparticles

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Abstract: The increasing resistance of bacteria to antibiotic agents is a main global public health problem. The use of nanoparticles is one of the promising ways to overcome microbial resistance to antimicrobial agents. Metal nanoparticles are increasingly used to target bacterial strains. Advances in nanotechnology, in particular the ability to synthesize nanoparticles of specific size and shape, are likely to lead to the development of new antibacterial agents. The antibacterial activities of nanoparticles are largely influenced by their sizes and large surface area/mass ratio. The antibacterial mechanisms of nanoparticles are poorly understood, but the currently accepted mechanisms include oxidative stress induction, metal ion release, and non-oxidative mechanisms. In this review, we have focused on the antibacterial activity of nanoparticles and their main mechanisms of action against bacteria. We also discuss the recent therapeutic strategies to control bacterial virulence and biofilm formation by targeting quorum sensing in bacteria without impeding bacterial growth. On the other hand, we reviewed five widely used databases of nanoparticles, aiming to provide the nanoscience community with valuable information about the specific content and function of these databases.

Keywords: nanoparticles; metal nanoparticles; antibacterial activity; antibacterial mechanisms; antimicrobial resistance; anti-quorum sensing; database.

1. Introduction

Bacterial infections remain one of the leading causes of morbidity and mortality worldwide. According to the report published by the World Health Organization, bacterial resistance to antimicrobial agents is a major global public health problem [1]. The absence of new effective antimicrobial agents is mainly associated with increased bacterial resistance. This has sparked initiatives worldwide to develop more effective antimicrobial compounds to address the problem of antimicrobial resistance [2–4].

The scientific community is highly concerned, and researchers are probing every possible way to overcome the antimicrobial resistance problem. One promising and important pathway is using nanoparticles to treat bacterial infections. Innovative advances in nanotechnology, in particular, the development of technology and techniques for synthesizing

NPs with specific characteristics, are likely to develop new nano-antimicrobials involving quorum sensing nano-inhibitors. In addition to their high surface/volume ratio [5,6], nanoparticles have specific physical, chemical, structural, mechanical, electrical, and optical properties that make them effective and promising antibacterial agents [7]. Furthermore, their ability to interact with the bacterial cell barrier, inhibition of bacterial protein and DNA synthesis, and the regulation of bacterial metabolic processes are important properties that attract scientists to this area of research and development [8].

Several types of NPs are currently used as antimicrobial agents. For example, silver (Ag), zinc oxide (ZnO), and titanium oxide (TiO_2) nanoparticles [9–13] show significant antimicrobial activities against several microorganisms [14–18]. As shown in Figure 1, a continuous increase in publications was observed, especially in the last few years. Silver nanoparticles got more importance for investigating applications as antimicrobial agents, primarily focusing on bacteria.

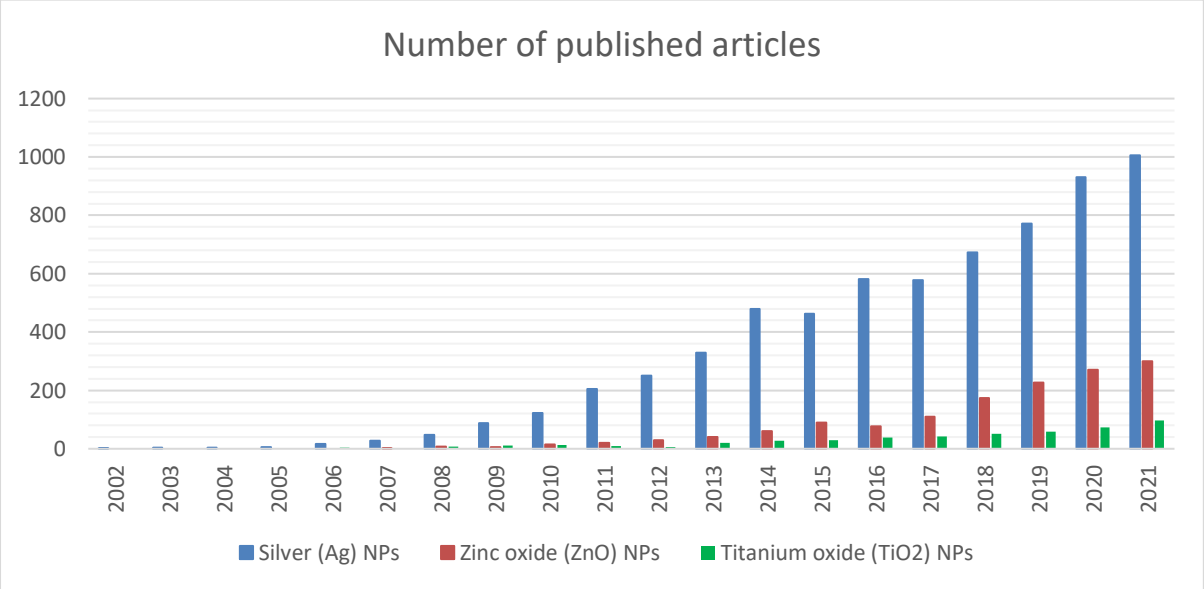

Figure 1. The number of published research articles on the antimicrobial activity of silver (Ag), zinc oxide (ZnO), and titanium oxide (TiO_2) nanoparticles. SCOPUS database was used, and antimicrobial activity of silver, zinc oxide, and titanium oxide were used as keywords.

The detailed antibacterial mechanisms of nanoparticles have not been fully explained. It is generally described as adhering to one of three models: formation of reactive oxidizing species (ROS) [19], metal ion release [20], and non-oxidative mechanisms [21]. It is also suggested that these three types of mechanisms can occur simultaneously. Another mechanism through which metal and metal oxide nanoparticles reduce the formation of biofilms and virulence of bacteria is the interruption in quorum sensing (QS), a bacterial gene expression system regulated by small signaling molecules [22–26].

Many reviews about NPs synthesis, types, and antimicrobial activities are reported exhaustedly elsewhere[27–33]. Hence, this review intends to provide a valuable reference for researchers interested in using nanoparticles to develop nano-antimicrobials. In this review, we discuss the synthesis of nanoparticles, including chemical, physical and biological synthesis methods. We also discuss the methods for the characterization of nanoparticles. More importantly, we discuss the biological applications of metal and metal oxide NPs, such as silver (Ag) NPs, zinc oxide (ZnO) NPs, and titanium dioxides (TiO_2) NPs, focusing on antibacterial mechanisms and anti-quorum sensing properties. Finally, we discuss the widely used databases to process the information on nanoparticle structure and physicochemical characteristics.

Understanding the function and available data in these databases is needed for scientists to retrieve specific information for research on nanomaterials.

2. Bacteria Resistance

2.1. Antibiotic resistance.

Antibiotic resistance is the most difficult medical challenge in treating infectious diseases. In the first few uses of antibiotics, resistance issues were marginal. However, the overuse of antibiotics has made it possible to select resistant organisms that colonize and induce difficult-to-treat infections. When bacteria become resistant to several types of antibiotics, called multidrug-resistant (MDR), treating these kinds of infections is extremely difficult [34,35].

Three groups of antibiotic-resistant pathogens emerge as major health problems [34]. The first group contains the methicillin-resistant strain *Staphylococcus aureus* (MRSA), which causes 19,000 deaths per year in the USA [36]. The cell membrane of this Gram-positive bacteria is mainly composed of a thick layer of peptidoglycan macromolecule (the main target of antibiotics), the periplasmic space, and the plasma membrane.

The second group of pathogens includes multidrug-resistant Gram-negative bacteria (MDR), which are less common than MRSA but present a serious threat to the onset of incurable diseases [34]. These different strains are resistant to some or all types of antibiotics commonly used to treat Gram-negative bacterial infections. The search for new effective antibiotics is made difficult because gram-negative bacteria can block all entry of antibiotics. If certain antibiotics manage to cross this barrier, the efflux pumps expel them [37]. On the other hand, Gram-negative bacteria have a different membrane from Gram-positive bacteria. Their membrane comprises an outer membrane, a thin layer of peptidoglycan, the periplasmic space, and a plasma membrane.

The third group of resistant pathogens contains other MDRs in addition to the ultra-resistant Mycobacterium tuberculosis strain (XRD-TB or MDR-TB), one of the greatest threats in developing countries. Treatment for MDR-TB requires two years of antibiotics, accompanied by serious side effects. XRD-TB is more difficult to treat and often fatal [37].

2.2. Bacterial resistance to nanoparticles.

In contrast to traditional antibiotics, nanoparticles can overcome existing antibiotic resistance mechanisms. NPs have characteristic dimensions <100 nm. The physical and chemical properties of nanoparticles, such as morphology and size, which range from 1 to 100 nm, are the main reasons NPs can effectively overcome microbial resistance and be considered an alternative to antibiotics [38,39]. The smaller the size and spherical the NPs are, the greater the surface-volume ratio is achieved, which helps to enhance the nanoparticles' antimicrobial activities [40].

3. Antibacterial Nanoparticles

With the problems of resistance to antimicrobial agents, nanoparticles have become a promising strategy for destroying bacteria. Nanoparticles (NPs) are defined as particles having a size of the nanometric scale (between 1 and 100nm) [41–43]. The application of nanomaterials as new antimicrobials could provide modes of action and different cellular

targets compared to conventional antibiotics. NPs can be organic or inorganic; however, inorganic NPs are the most widely used due to their ability to withstand adverse reaction conditions [44]. Several types of NPs, including nanoparticles of metals and metal oxides, have been developed and evaluated by different researchers; examples include silver (Ag), zinc oxide (ZnO), and titanium dioxide (TiO_2). Nanoparticles act on bacteria by several different methods, and the mode of action of these NPs varies with each different type (Table 1).

Table 1. Mode of action of various nanoparticles against pathogenic microbes.

Type of NPS	Mode of action	Bacterial strains	References
Silver (Ag)	- Inhibition of DNA replication and the respiratory chain in bacteria and fungi. - Creation of reactive oxygen species. - Inhibit the formation of the cell wall of gram-positive bacteria.	- *S.aureus* - *P.aeruginosa* - *E.coli*	[45,46]
Zinc oxide (ZnO)	- Hydrogen peroxide generated on the surface of the ZnO penetrates into bacterial cells and disrupts their metabolism. - Zn^{2+} ions released during the dissolution of the nanoparticles damage the cell membrane and interact with intracellular components. - Formation of reactive oxygen species. - Disruption to the bacterial cell membrane.	- *E.coli* - *S.aureus* - *P.aeruginosa*	[47–51]
Titanium dioxide (TiO_2)	- Formation of superoxide radicals, ROS, and site-specific DNA damage.	- *E.coli* - *S.aureus*	[17,52]

3.1. Synthesis of antibacterial nanoparticles.

As shown in Figure 2, nanoparticles can be synthesized using bottom-up or top-down methods [53,54]. The top-down method is based on physical or chemical processes, while combined chemical and biological synthesis are used in bottom-up approaches [55,56]. In the bottom-up approach, NPs are built atom by atom or molecule by molecule. In contrast, in the top-down approach, a large structure is gradually undersized, reaching nanometric dimensions after applying severe mechanical/chemical stresses, strong shocks, and strong deformations.

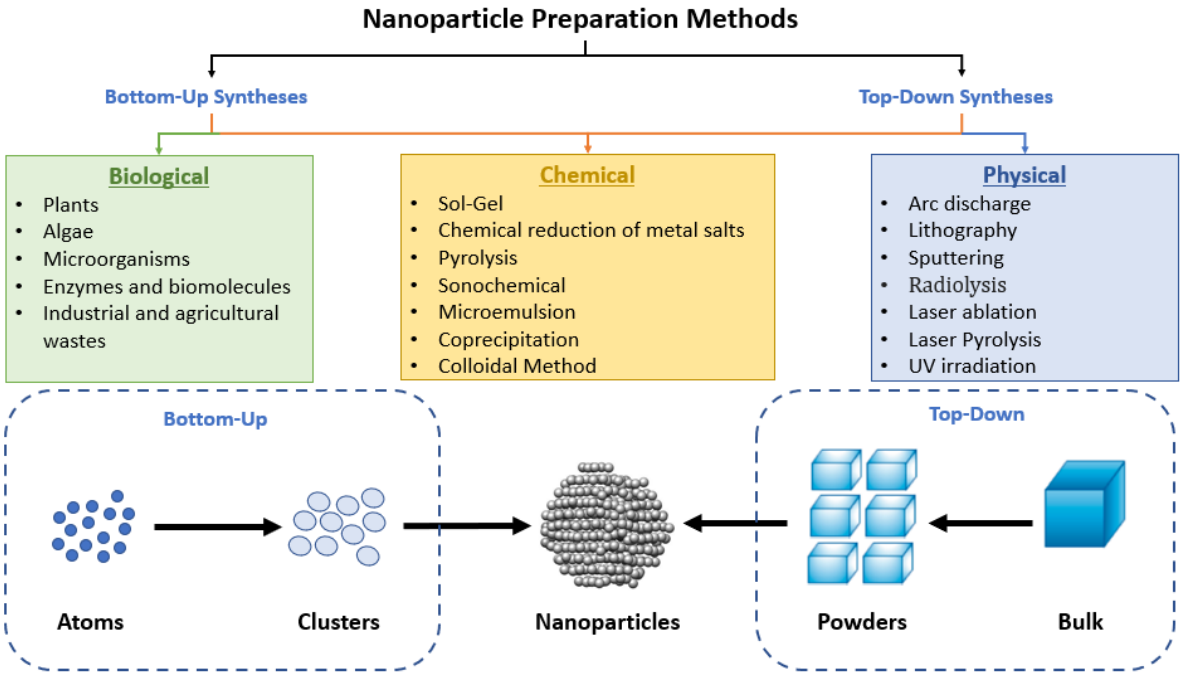

Figure 2. Different approaches and methods for nanoparticle synthesis. Nanoparticles can be synthesized through chemical, physical, and biological routes.

The "bottom-up" approach consists of building nanomaterials atom by atom, molecule by molecule, or aggregate by aggregate. The assembly or positioning of atoms, molecules, or aggregates is carried out precisely, controlled, and exponentially, thus allowing the development of functional materials whose structure is completely controlled [54].

The "top-down" approach stems from microelectronics and consists of reducing and, more precisely, miniaturizing current systems by optimizing existing industrial technologies. Thus, devices and structures are gradually undersized or fractionated until they reach nanometric dimensions. Currently, high-energy grinding is one of the main techniques used in this approach [54].

The two approaches tend to converge in terms of the size range of NPs. The "bottom-up" approach nevertheless seems richer in terms of the type of material, diversity of architecture, and control of the nanometric state, while the "top-down" approach makes it possible to obtain important quantities of material, but the control of the nanometric state turns out to be more delicate.

3.2. Characterization of nanoparticles.

3.2.1. Size measurement.

The most widely used methods are electron microscopy methods, X-ray diffraction, and dynamic light scattering (DLS) [57].

3.2.1.1. Microscopic methods.

Electron microscopy uses an electron beam to image structures that cannot be seen with the naked eye or with optical microscopy. Two methods of electron microscopy are mainly used:

- Scanning electron microscopy (SEM).

Among various electron microscopy techniques, SEM is a surface imaging method fully capable of resolving different particle sizes, size distributions, nanomaterial shapes, and the surface morphology of the synthesized particles at the micro and nanoscales [58,59]. The disadvantage of SEM is that with this technique, we cannot identify the particle's internal structure, but the main advantage is that it can deliver valuable information regarding the purity and degree of particle aggregation [60].

- Transmission electron microscopy (TEM).

The TEM microscopy allows measurements of size, shape, and count as well as the state (agglomerated, aggregated) of nanoparticles with nanometric resolution. TEM has two advantages over SEM: it can provide a better spatial resolution and the capability for additional analytical measurements [61,62]. The disadvantages of TEM include the need for a high vacuum and a large sample section [63].

3.2.1.2. X-ray diffraction (XRD).

X-ray crystallography or X-ray diffraction (X-ray diffraction) is an analysis technique based on the diffraction of X-rays on the matter. Since diffraction only occurs on a crystalline material, we also speak of radio crystallography. Diffraction is one of the elastic scattering methods [64]. This method uses an incident x-ray beam of known wavelength, which encounters the crystal causing the light beam to scatter in specific directions. By measuring the

angles and the intensity of the refracted rays, it is possible to obtain a three-dimensional image of the electron density in the crystal. From this density, we obtain two types of information [65–67]:

- Structural information: Lattice parameters, atom distribution,
- Microstructural information: Grain size.

The disadvantages of this XRD technique are that sometimes there is difficulty in growing the crystals and the ability to get results pertaining only to a single conformation/binding state [68].

3.2.1.3. Light scattering methods.

The static method (SLS): Static light scattering is a technique for measuring absolute molar mass from the relationship between the intensity of light scattered by a molecule and its size and molar mass, as described by Rayleigh's theory. In other words, according to Rayleigh's theory, large molecules scatter more light for a given light source than small ones, and the scattered intensity is proportional to the molar mass of the molecule [69].

The dynamic method (DLS): The DLS consists in measuring the hydrodynamic diameter of the particle. The scattering of light by the particles in the sample is subjected to random thermal movements [69].

3.2.2. Stability of nanoparticles: zeta potential

The measurement of the zeta potential makes it possible to evaluate the stability of colloidal suspensions [70]. Zeta potential is defined by the electrical charge that a particle acquires from the cloud of ions surrounding it when a particle is in motion [71]. The value of zeta potential greater than +30 mV or less than −30 mV means that the colloidal suspension is highly stable [31]. In fact, colloidal suspensions stability and aggregation propensity are issues that should be strongly considered profoundly. Aggregation might cause a substantial decrease in the effective surface area of nanoparticles, which can lead to the reduction or loss of antibacterial activity [72].

3.2.3. Specific surface area.

The specific surface area, defined as the total surface area of a solid material per unit of mass, is an important characteristic of nanoparticles that is partly responsible for their properties. The specific surface area also makes it possible to determine the volume-specific surface area (VSSA) that could replace or complete the size measurement by electronic micro copying [73,74]. The most used technique for determining the specific surface is the Brunauer, Emmett, and Teller method (BET) [75]. This technique models the physical adsorption (physisorption) of gas molecules on a solid surface in a closed system. Physisorption is a phenomenon that occurs in any gas-solid or gas-liquid system when the temperature and pressure conditions are adequate.

Particle size and specific surface area are essential parameters that play a crucial role in interacting nanomaterials with the bacterial surface. As a particle's size decreases, its specific surface area increases, and the number of atoms on the surface becomes more considerable [76]. Nanoparticles became highly active against bacteria due to their antibacterial activity because their large surface area gives for multivalent interactions with the bacterial surface [77].

3.3. Antibacterial mechanisms of NPs.

The lethal mechanism of nanoparticles is still under discussion, but three main mechanisms are assumed (Figure 3), namely; first, the formation of reactive oxygen species (ROS) [19]; second, the ion release process [20]; and, finally, non-oxidative mechanisms [21].

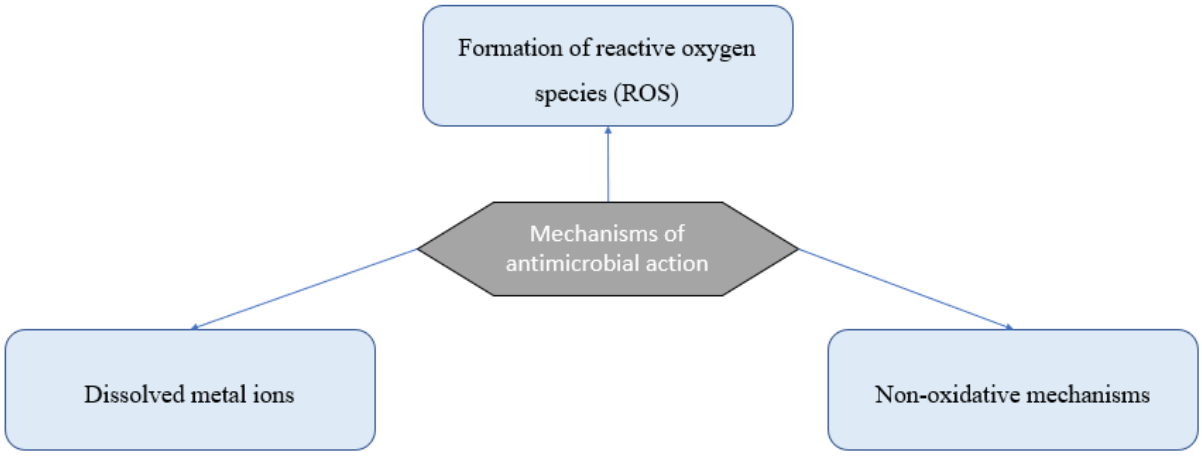

Figure 3. The antibacterial mechanisms of nanoparticles.

3.3.1. Formation of reactive oxygen species (ROS).

Reactive oxidizing species (ROS) production by nanoparticles plays an important role in their antibacterial efficacy. The level of ROS production induced by NPs is controlled by several factors such as size, shape, surface, solubility, aggregation, composition, and particle uptake [7,78,79]. Metal and metal oxide NPs usually produce reactive oxygen species (ROS) by releasing metallic ions that alter the cellular components of bacteria [80,81]. ROS are made up of short-lived oxidants, such as superoxide radicals (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and singlet oxygen (O2 •) [82,83]. Due to the high reactivity of these species, ROS can damage (1) cell membrane, resulting in membrane rupture and cell death [84]. Furthermore, excessive cellular ROS could cause damage to (2) mitochondrial, which is a known trigger of the apoptotic pathway [85]. In addition, ROS could cause (3) nucleic acid damage [86] and can also be the origin of (4) protein damage, leading to vitiation and/or abolition of protein functions [87] (Figure 4).

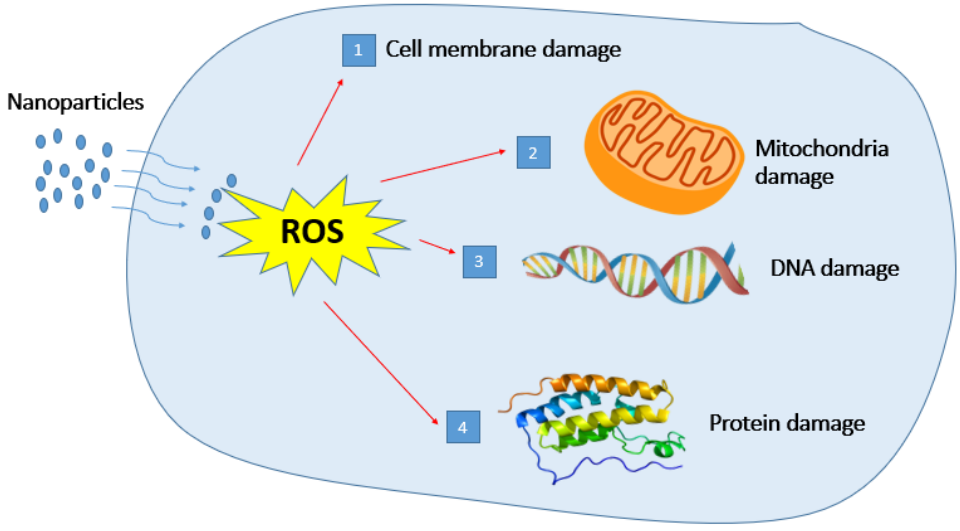

Figure 4. Schematic representation of ROS mechanisms of NPs against bacteria.

Potential antibacterial properties of some metal and metal oxide NPs (such as silver [Ag] nanoparticles, titanium dioxide [TiO_2], and zinc dioxide [ZnO]) have been widely reported against both Gram-negative and Gram-positive bacteria [5,88–91]. For example, silver nanoparticles can generate high amounts of ROS: singlet oxygen, hydroxyl radical, superoxide anion, hypochlorous acid, and hydrogen peroxide [92]. Whereas zinc oxide NPs can generate hydrogen peroxide and hydroxyl radicals but not superoxide radicals [8]. In addition, TiO_2 NPs can produce ROS—such as hydroxyl radical (·OH), singlet oxygen (O_2), and hydrogen peroxide (H_2O_2)—being generated [93].

3.3.2. Dissolved metal ions.

Metal ions are slowly released from the metal oxide and are absorbed through the cell membrane, followed by direct interaction with functional groups such as [mercapto (–SH), amino (–NH), and carboxyl (–COOH)]. These interactions have several consequences, including damaging enzymatic activity, modification of physiological processes, and inhibition of microorganisms [94]. A study by Polivkova *et al*. showed that silver nanowires release silver ions in solution and also have antibacterial effects [95]. However, other studies have suggested that the main antimicrobial mechanism of NPs is not due to the release of metal ions from NPs, as solutions of metal ions cause only weak antibacterial activity [96,97].

3.3.3. Non-oxidative mechanisms.

The non-oxidative mechanism involves the direct interaction of nanoparticles with bacterial membranes or cell walls. The non-oxidative mechanism also affects the inactivation of microbes by decreasing the critical cellular metabolism such as protein, amino acid metabolism, nucleotide metabolism, energy metabolism, and carbohydrate metabolism without oxidative stress induction. Leung and colleagues demonstrated the antimicrobial activity of three types of nanoparticles (MgO-NPs) against *E. coli* [21]. The three types of MgO NPs have been confirmed to have good antibacterial effects on *E. coli* under UV and natural light. However, these antibacterial mechanisms of NPs are unrelated to membrane lipid peroxidation caused by oxidative stress [21].

3.4. Examples of nanoparticles with antibacterial activity.

Several metal or metal oxide NPs, such as silver (Ag) NPs, zinc oxide (ZnO) NPs, and titanium dioxides (TiO_2) NPs, are known to have antimicrobial activities against both Gram-positive bacteria and Gram-negative bacteria.

Silver NPs (AgNPs): silver nanoparticles are recognized as a promising strategy against several Gram-negative and Gram-positive species, such as *P. aeruginosa*, *S. aureus*, and *E. coli*, since it disrupts both cell wall and metabolic pathways [98,99]. Several authors have reported that the antibacterial activity of AgNPs is influenced by the size of the NP. Antibacterial activity increases upon reduction of their particle size due to the increase in the surface area, which allows greater contact with bacterial cells [45,100,101]. The antibacterial activity of AgNPs with sizes (5 to 20 nm) has a strong antimicrobial activity against *S. aureus* [102]. AgNPs exhibited high bactericidal activity against multidrug-resistant *Pseudomonas aeruginosa*, and ampicillin-resistant *E. coli* O157:H7. The minimum inhibition concentration (MIC) was found to be 83.3 mM for *P. aeruginosa* and *E. coli* O157:H7 [103]. Increasing scientific evidence has demonstrated that AgNPs activity depends not only on their size [104]

but also on their shape. The shape is the other parameter of NPs that are responsible for the interaction with the bacterial cell wall. Truncated triangular-shaped silver nanoparticles exhibited higher antibacterial activity against *E. coli* bacteria rather than spherical and rod-shaped NPs [105,106].

Zinc Oxide (ZnO) NPs: ZnO NPs fight against bacteria [106], fungi [107], and viruses [108]. The mechanism of ZnO NPs' antimicrobial activity involves the liberation of antimicrobial ions, mainly Zn2+ ions [109–111], and the generation of reactive oxygen species [112,113]. ZnO generates highly reactive oxygen species such as hydrogen peroxide (H_2O_2) and OH^-. Hydrogen peroxide generated on the surface of ZnO can penetrate bacterial cells and effectively inhibit cell growth [48]. However, Zn^{2+} ions released from the ZnO NPs significantly affect the damage of the cell membrane, the active transport inhibition, the amino acid metabolism, and the enzyme system disruption. Kasemets *et al*. [109] have shown that the release of Zn^{2+} ions was a logical cause of ZnO toxicity toward *Saccharomyces cerevisiae* cells [114]. Previous studies have indicated that ZnO NPs exhibit antibacterial activity against *E. coli*, *Listeria monocytogenes*, *Salmonella*, and *Staphylococcus aureus* [18,49].

Titanium Dioxide (TiO_2) NPs: TiO_2 is a non-toxic and chemically stable molecule with specific optical properties [97] and has significant antibacterial activity against certain microbes [115]. The antimicrobial activity of TiO_2 is due to its size, crystalline structure, and shape [116]. Anatase has the most antibacterial activity among the three crystal structures (anatase, brukide, and rutile). Anatase structures produce hydroxyl radical (•OH) via a photocatalytic reaction, puncturing the bacterial wall and killing the bacteria. Besides, the antibacterial properties of nanoscaled titanium are also related to its photocatalytic properties. It was demonstrated, *in vitro*, that TiO_2-mediated photocatalytic had microbial activity against facultative anaerobes (*E. coli*, *S. aureus*) and obligate aerobes (*P. aeruginosa*) [117]. Like other metal oxides, TiO2 acts on bacteria by forming reactive oxygen species (ROS) [118]. The ROS synergistically acts on phospholipids on the surface of bacteria [119], causing site-specific DNA damage [17].

3.5. Anti-quorum sensing activity of nanoparticles.

Quorum sensing (QS) is a mode of bacterial communication that allows bacteria to synchronize their genetic expressions according to their cell densities through the production, release, accumulation, and detection of small signal molecules called autoinducers (AIs) [120,121]. For example, Gram-positive bacteria produce autoinducing peptides (AIPs), whereas Gram-negative bacteria produce acyl-homoserine lactone (acyl-HSLs) signal molecules. These signal molecules (AIs) stimulate the expression of QS several genes that lead to many bacterial functions such as biofilm formation, virulence factor production, antibiotic resistance, bioluminescence, biosurfactant production, swarming, etc. [122].

Targeting QS systems in bacterial pathogens is a promising strategy to control bacterial virulence and biofilm formation without impeding bacterial growth [120]. Several quorum quenching (QQ) strategies have been proposed (as illustrated in Figure 5) to disrupt cell-to-cell communication by inhibiting the synthesis of signaling molecules, degradation of a signaling molecule, inhibition of signaling molecule-receptor complex formation, and inhibition of expression of QS-regulated genes [123–125].

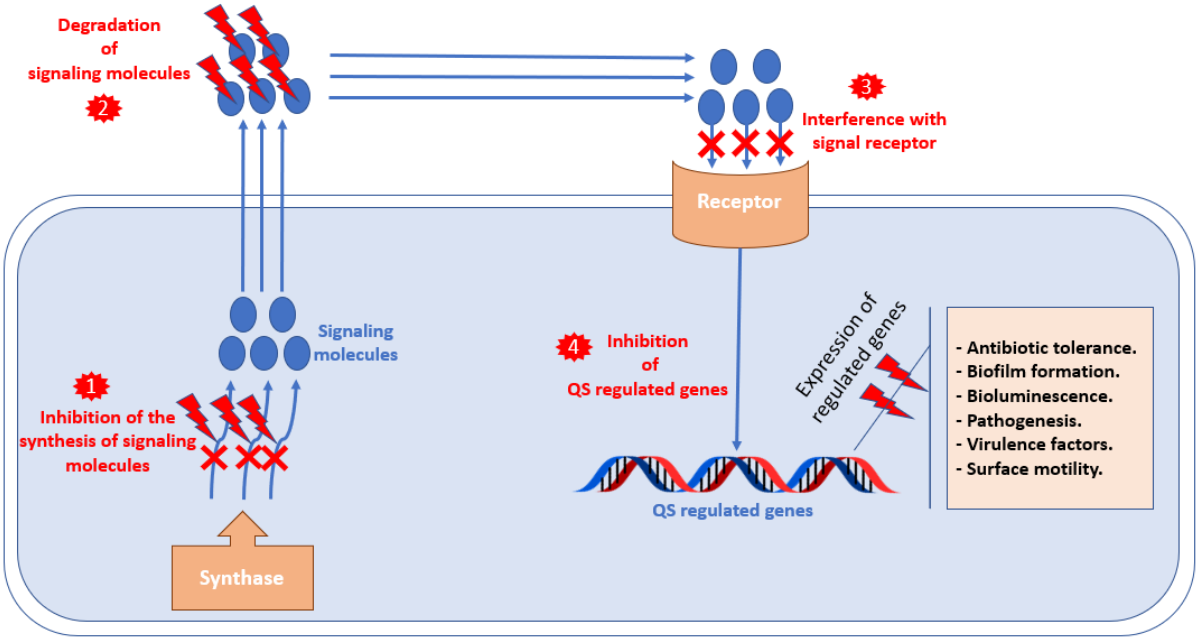

Figure 5. Schematic representation of anti-quorum sensing mechanisms of nanoparticles.

The recent advancement in nanotechnology has facilitated the development of novel nano-antimicrobials targeting the QS mechanism with less toxicity and improved therapeutic potential (Table 2). Ali *et al*. [126] reported that AgNPs have the potential to block the synthesis of N-acyl homoserine lactones (signaling molecules) by inhibiting LasI/RhlI synthase. AgNPs had the potential to inhibit the quorum sensing of *P. aeruginosa*. Saleh, M. M. *et al.* [127] revealed that ZnO nanoparticles had a statistically significant reduction in the production of QS-controlled virulence factors such as rhamnolipids, pyoverdin, pyocyanin, hemolysins, proteases, and elastase. Furthermore, ZnO nanoparticles exhibited a significant down-regulate the relative of QS-regulatory genes lasI, lasR, rhlI, rhlR, pqsA and pqsR. Similar results have been obtained by Singh *et al*. [128] that silver nanoparticles down-regulated the expression of quorum-sensing-regulatory genes lasI, lasR, rhlI, and rhlR. In another study, Garcia-Lara *et al*. [129] reported that ZnO NPs could significantly reduce the secretion of quorum-sensing dependent pyocyanin and elastase and the production of biofilm in *P. aeruginosa*.

Table 2. Metals and metal oxide nanoparticles demonstrate anti-QS activity and their mode of action.

Nanoparticles	Test organism	Mode of action	References
Silver NPs (AgNPs)	*P. aeruginosa* (Gram-negative)	- Inhibition of LasI/RhlI synthase blocked the biosynthesis of N-acyl homoserine lactones (AHLs); thus, no AHL was produced, and no QS occurred. (*In silico* approach)	[126]
		- Molecular modeling and docking studies showed that silver nanoparticles had the potential to inhibit key enzymes (LasR, Vfr, QscR, RhlR, and PqsA) that are involved in QS.	[130]
		The AgNPs efficiently inhibited the production of quorum sensing mediated virulence factors viz. protease, pyocyanin, hemolysin, and biofilm formation by *P. aeruginosa*.	[131]
	S. aureus (Gram-positive)	- The silver nanoparticles effectively inhibited the quorum-sensing mediated biofilm formation in *S. aureus.*	[132]
	C.violaceum (Gram-negative)	- Inhibition of violacein and alginate productions was reduced by 89.6 and 75.6% at 4 and 8 µg/mL of silver nanoparticles, suggesting anti-quorum sensing activity. (*In vitro* approach)	[130]
	P. mirabilis and *S. marcescens* (Gram-negative)	- The *Piper betle*-based synthesized silver nanoparticles (NPs) could inhibit QS-regulated virulence factors such as prodigiosin, protease, biofilm formation, hydrophobicity, and exopolysaccharides production in uropathogenic. - The gene expression analysis disclosed that silver nanoparticles downregulation the expression of *flhD* and *bsmB* genes in *S. marcescens* and *flhD* and *rsbA* genes *in P. mirabilis.*	[133]

Nanoparticles	Test organism	Mode of action	References
Zinc Oxide (ZnO) NPs	*P. aeruginosa* (Gram-negative)	- The interaction of ZnO NPs with the QS (Las/Rhl) systems of *P. aeruginosa* led to the inactivation of autoinducers such as N-acyl homoserine lactone (AHL) molecules, which ultimately led to QS inactivation and down-regulation negative of virulence determinants. (*In silico* approach) - The ZnO NPs effectively inhibited the growth and quorum-sensing mediated virulence in *P. aeruginosa*, such as swarming, swimming, and biofilm formation. (*In vitro* approach)	[134]
		- Synthesized ZnO nanostructures significantly inhibited QS-regulated functions of *C. violaceum* CVO26 (violacein) and protease, elastase, alginate, and pyocyanin production in *P. aeruginosa* PAO1 significantly.	[135]
		- The ZnO nanoparticles inhibit biofilm formation and pyocyanin production without affecting the growth of planktonic cells.	[136]
		- The ZnO nanoparticles showed inhibition of the production of QS-controlled virulence factors pyocyanin, rhamnolipids, pyoverdin, hemolysins, proteases, and elastase.	[127]
	C. violaceum (Gram-negative)	- The ZnO nanoparticles lowered the expression of the genes responsible for quorum sensing in *C. violaceum*, bringing about inhibition of N-acyl homoserine lactone (AHL) synthase, and in response blocking quorum sensing in *C. violaceum*.	[137]
Titanium Dioxide (TiO_2) NPs	*P. aeruginosa* (Gram-negative)	- Titanium dioxide nanoparticles showed a significant reduction in biofilm formation of *P. aeruginosa* strains (96%) and also a reduction in the expression of genes regulated by quorum sensing (*lasR, lasI, rhll, rhlR , pqsA , pqsR*).	[138]

Targeting quorum sensing and biofilm formation by metals and metal oxide nanoparticles can be used as a novel strategy in developing antibacterial agents that can counter cell-to-cell communication, prevent biofilm production, bypass resistance to antibacterial agents, and prevent bacterial infections.

4. Nanoparticles databases

An overview of nanomaterials databases is provided in Table 3. The emergence of recent databases such as caNanoLab (cancer Nanotechnology Laboratory), eNanoMapper, Nanomaterial Registry (NR), Nanoparticle Information Library (NIL), and PubVINAS seems encouraging and is discussed below [139–143].

The caNanoLab is a database created by the National Cancer for sharing information within the international biomedical nanotechnology research community to accelerate and validate the use of nanoparticles in biomedicine. The caNanoLab contains detailed information on characterizations (physicochemical, *in vitro*, *in vivo*, and *ex vivo*), composition, experimental design, and publications of nanoparticles. The physicochemical properties of nanoparticles include size, shape, composition, purity, molecular weight, and surface area. In addition, experimental biological data such as genotoxicity, oxidative stress, cytotoxicity, immunotoxicity, and pharmacokinetics are collected in this database [144].

The eNanoMapper is an online database hosting nanoparticle characterization data and biological and toxicological information. In eNanoMapper, physicochemical properties such as stability, size distribution, zeta potential, surface area, freezing/melting point, shape, and aspect ratio are included. eNanoMapper also contains a variety of toxicological experimental data such as immunotoxicity, cell viability, genetic toxicity, and oxidative stress [145].

The Nanomaterial Registry (NR) is a public and wholly curated database that is funded by the National Institutes of Health (NIH). It archives experimental data such as physicochemical characteristics such as composition, size, shape, surface area, surface chemistry, solubility, stability, aggregation/agglomeration state, surface charge, and size distribution), and studies on biological interactions and environmental interactions studies of

nanoparticles. In this database, the nanomaterials can be browsed by their material type (for example, carbon, polymer, metal, metal oxide), size (for example, less than 25 nm, 25–74 nm, 75–149 nm, 150–300 nm, and greater than 300 nm), shape (1D, 2D, and 3D), or surface area (for example less than 10 m^2/g, 10–49 m^2/g, 50 - 150 m^2/g, greater than 150 m^2/g) [146].

The Nanoparticle Information Library (NIL) is a prototype searchable data resource on nanoparticle properties associated with nanoparticle health and safety. It contains information on nanomaterial composition, production method, surface area, particle size, morphology including scanning, transmission, or other electron micrographic images, availability for research or commercial applications, and associated or relevant nanoparticle publications [145].

The PubVINAS is a nanoparticles database that contains several types of nanoparticles such as silver nanoparticles (AgNPs), metal oxide nanoparticles (MONPs), gold nanoparticles (GNPs), platinum nanoparticles (PtNPs), palladium nanoparticles (PdNPs), quantum dot nanoparticles, DNA origami nanoparticles (DnaNPs), and carbon nanoparticles. The PubVINAS contains the physicochemical properties (size, shape, number of ligands, log P, and zeta potential) and biological activities (cytotoxicity, cell uptake, cell viability, cell association, and oxidative stress) of nanoparticles [147].

Table 3. Databases of nanoparticles.

Database	Website	Description
caNanoLab	https://cananolab.nci.nih.gov/	- Nanotechnology in biomedicine
eNanoMapper	https://data.enanomapper.net/	- Safety assessment of nanomaterials
Nanomaterial Registry (NR)	https://nanomaterialregistry.net/	- Physico-chemical properties - Biological interaction studies - Environmental interaction studies
Nanoparticle Information Library (NIL)	http://nanoparticlelibrary.net/	- Physicochemical characteristics
PubVINAS	http://www.pubvinas.com/	- Physico-chemical properties

The databases presented above provide a solid foundation to support data analysis on nanoparticles' physical, chemical, and biological properties, but they currently house small amounts of data. This could be partly due to the inefficiency of data-sharing and collection processes. This reflects a discrepancy between the data generated in the researchers' laboratories and those available in the databases.

5. Conclusions

The evolution of bacterial resistance to antimicrobial agents poses a great global public health problem, and new antimicrobial agents are urgently sought to address this problem. Innovative advances in nanotechnology, particularly nanoparticle engineering, are likely to lead to the development of new antibacterial agents. Different research groups have developed several such nanoparticles, and their antimicrobial activity, anti-quorum sensing, and anti-biofilm have been tested on Gram-positive and Gram-negative bacteria. However, the advantages of NPs are the same reasons that make them dangerous, small size, surface properties, and aggregation. Therefore, research into nanoparticles is currently one of the most studied branches of science due to the almost unlimited fields of application.

Publicly accessible databases are core resources for data-rich research, consolidating field-specific knowledge and highlighting best practices and challenges. Further effective growth of nanoparticle databases requires the concerted efforts of database stewards, the research community, journal publishers, and funding agencies.

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Conflicts of Interest

The authors declare no conflict of interest.

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