

Antibacterial Activity of Nanoparticle Biosynthesis by Bacteria

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النشاط المضاد للبكتيريا للتخليق الحيوي للجسيمات النانوية بواسطة البكتيريا

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Received: 2 /4/2023 Accepted: 24/5/2023 Published: 30/6/2023

Abstract

Background: The world's most common cause of illness and death is still bacterial infections. According to a World Health Organization report, bacterial resistance to antibiotics poses a serious threat to global public health. In recent years, the use of nanoparticles (NPs) as an antibiotic alternative has increased. **Results:** Due to the nanoparticles' inherent antibacterial activity, metal and metal oxide nanoparticles are the most promising nanomaterials for biological applications. Although nanoparticles have intriguing antibacterial properties, their use in medical applications is currently restricted due to the lack of clear understanding of the mechanisms underlying their action. **Conclusion:** The main focus of this review was the interactions between bacteria and the antibacterial capabilities of nanoparticles. Membrane contact, cation release, biomolecule oxidation, production of reactive oxygen species, and reactive oxygen species are some ways bacteria can kill themselves. Examining how NP affects gene and protein regulation patterns (transcriptomic and proteomic) is crucial.

Keywords: bacterial resistance, antibacterial processes, nanotechnology, and nanomedicine.

الخلاصة:

الخلفية: لا تزال العدوى البكتيرية هي السبب الأكثر شيوعاً للمرض والوفاة في العالم. وفقاً لتقرير منظمة الصحة العالمية، تشكل مقاومة البكتيريا للمضادات الحيوية تهديداً خطيراً للصحة العامة العالمية. في السنوات الأخيرة، زاد استخدام الجسيمات النانوية كبديل للمضادات الحيوية.

النتائج: نظراً لنشاط الجسيمات النانوية المضاد للبكتيريا المتأصل، فإن الجسيمات النانوية المعدنية وأكسيد المعادن هي أكثر المواد النانوية الواعدة للتطبيقات البيولوجية. على الرغم من أن للجسيمات النانوية خصائص مضادة للبكتيريا مثيرة للاهتمام، إلا أن استخدامها في التطبيقات الطبية مقيد حالياً بسبب عدم وجود فهم واضح للآليات الكامنة وراء عملها.

الخلاصة: كان التركيز الرئيسي لهذه المراجعة على التفاعلات بين البكتيريا والقدرات المضادة للبكتيريا للجسيمات النانوية. ملامسة الغشاء، إطلاق الكاتيون، أكسدة الجزيئات الحيوية، إنتاج أنواع الأكسجين التفاعلية، وأنواع الأكسجين التفاعلية هي بعض الطرق التي يمكن للبكتيريا ان تقتل بها نفسها. يعد فحص كيفية تأثير الجسيمات النانوية على أنماط تنظيم الجينات والبروتينات (النسخية والبروتينية) امراً بالغ الأهمية.

الكلمات المفتاحية: المقاومة البكتيرية، آليات مضادة للجراثيم، تكنولوجيا النانو، طب النانو.

1. Introduction



Each year, millions of individuals throughout the world experience sickness and mortality due to microbial pathogenesis (1). Soon after their discovery, Before the establishment of bacterial drug resistance, antibiotics were widely acknowledged as an efficient treatment for illnesses. Recently, numerous strategies to treat antibiotic resistance have been created in an effort to discover fresh, broad-spectrum medications with protracted half-lives (2). The concept of using nanoparticles as cutting-edge, unconventional antibacterial agents has been one of these methods (3). Current developments in nanotechnology have produced nanoparticles that have been proven to be powerful, all-purpose antibacterial agents (4) To create biodegradable nanoparticles with diameters ranging from 1 to 100 nm, metals or metal oxides are biologically reduced to their elemental states (3,5).

At low concentrations, nanoparticles (NPs) deliver efficient, focused, and long-lasting antibacterial effects (6). Since they are more compact and have a larger surface area -to- volume ratio than bacteria, metallic nanoparticles interact with bacteria and biofilms in a major antibacterial way (7). The ability of metal-based NPs to prevent bacterial growth is evaluated critically. An extensive review of the literature on bacterial interactions with metal and metal-oxide NPs is done to determine their potential as antibacterial agents. Nanomedicine greatly improves the stability and physicochemical properties of antibiotics, increasing the potency of already-approved medications. Compared to equal-free drugs, adverse effects are reduced by prolonging antibiotic release, internalizing biofilms, adjusting the dose to the site of infection, and increasing systemic circulation (6, 8).

The ongoing rise in bacterial resistance has forced researchers to create new antibiotic medications. Metal NPs are one of the most promising of these new antibiotic drugs, having demonstrated exceptional antibacterial activity in numerous trials. Furthermore, the functionalization, surface/volume ratio, size, and form of the surfaces influence the metal nanoparticles' biocompatibility and bactericidal properties, which are both crucial to their antibacterial effect. Through the use of nanotechnology, NPs can be created to have acceptable physicochemical properties in order to lessen their cytotoxic effects and the risk associated with their use in biological applications (9, 10). The primary subjects of this review are the mechanisms of bacterial resistance and the antibacterial properties of nanoparticles. Research into fundamental antimicrobial processes is necessary to produce more effective antibacterial agents.

2. How Nanoparticles Work Against Microbes

By utilizing the bacterial metal transport system and metalloproteins, metallic NPs and antibiotic-like compounds may be able to distinguish between eukaryotic (cells found in mammals) and prokaryotic (cells found in bacteria) cells. Contrary to antibiotics, metal-based NPs increase bactericidal activity in a variety of ways. According to (1), silver nanoparticles derived from the Parmand *Aspergillus andotrema praesorediosum* can effectively suppress eight different pathogenic pathogens, including gram-positive and gram-negative bacteria. They found that the gram-negative bacterial growth was greatly inhibited by the antibacterial activities of silver nanoparticles generated from *P. praesorediosum*. According to **Siddiqi et.al.** (11), three gram-negative bacteria (*Escherichia coli*, *klebsiella*, *pseudomonas aeruginosa*) and six gram-positive bacteria (*Staphylococcus aureus*, *Streptococcus mutans*, *Streptococcus*



pyrogenes, *Streptococcus viridans*, and *Corynebacter*) *S. mutans*, *C. diphtheriae*, and *P. aeruginosa* are susceptible to the nanoparticles, whereas *E. coli* and *K. pneumoniae* are not. The antibacterial and antifungal characteristics of ZnO/TiO₂/SiO₂ and Fe₃O₄/SiO₂ nanocomposites driven by *Lecanora muralis* were studied by **Abdullah et.al.**(12).

who discovered that they were effective against three harmful microorganisms (*Pseudomonas sp.*, *Candida albicans*, and *S. aureus*). (*Candida albicans*, *Aspergillus flavus*, *Aspergillus niger*, and *Aspergillums terreus*). With a specific emphasis on the bacterial strains investigated, the mechanism of action, and the production processes used, there are three basic ways in which metal NPs physically interact with bacterial cells. Antibiotics and metal-based nanoparticles can differentiate.

2.1. Bilayer Phospholipid Interactions

By electrostatically adhering to the cell wall and/or releasing metallic ions, metal-based nanoparticles (NPs) can affect the potential and integrity of bacterial cell membranes (13). These interactions cause membrane rupture and increased oxidative stress, both of which lead to the destruction of bacterial proteins. A significant amount of water is released into the cytosol when the cell membrane is breached.

To try to make up for this loss, cells use proton efflux pumps and the transfer of electrons from bacteria. These transmembrane systems suffer significant harm from the extreme need for these ions (14). The result of this imbalance between the stability of the ions and the membrane is reduced respiration. A disruption in the energy flow, which leads to cell death (15). This effect has been demonstrated by the interaction of titanium oxide, silver, gold, zinc oxide, and magnesium oxide NPs. Silver nanoparticles preferentially interact with the parts of the cell membrane that contain sulfur to stop the formation of cell walls (13).

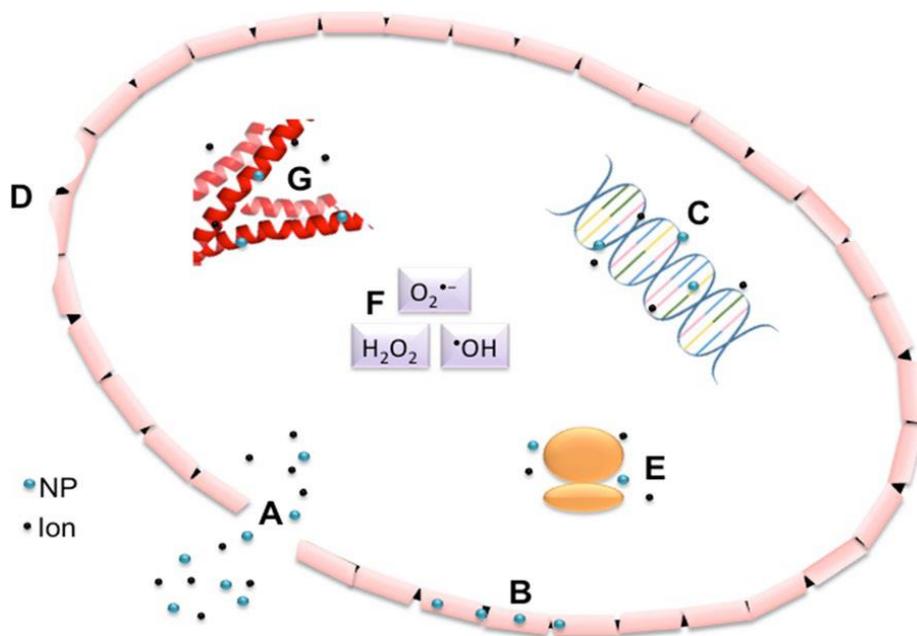


Fig. 1 An illustration of the conduct of NPs exposed to Gram-negative *E. coli* bacterium. (A) The disintegration of the cell wall enables the release of intracellular components. (B) The cytosol and membrane are beginning to drift apart as NPs enter the periplasm. DNA and NP interactions are (C). (Reactive oxygen species (ROS) generation may result from inhibition. Cell pits that develop upon exposure (D). (E) Improper DNA function, misaligned or suppressed proteins, and suppression of the normal ribosome activity all result in the production of ROS. ROS production is (F). interaction with proteins, particularly with cysteine (G).(13)

2.2 The section on Binding to Cytosolic Proteins Metallic-based NPs

by attaching to cytosolic proteins including DNA and enzymes, fight against pathogens. By the inhibition of the respiratory, metabolic, and ATP generation processes, this interaction decreases function. For example, silver binds to respiratory chain enzymes and DNA to prevent DNA replication and division (16). On the other hand, gold influences DNA by turning on cellular genes (17). As a result, the integrity of the membrane is harmed, and ROS start to build up in the cytoplasm of the cell.

2.3 Forming Reactive Oxygen Species, Section

By producing oxygen free radicals or reactive oxygen species (ROS), such as superoxide anions or hydrogen peroxide, NPs also kill bacteria (H_2O_2). The NPs themselves indirectly contribute to the generation of ROS. Significant oxidative stress and damage from ROS lead to lipid peroxidation. These adverse effects include altered proteins, enzyme inhibition, and RNA and DNA damage to the cell's macromolecules (14). This extreme oxidative stress may cause the bacterial membrane to develop holes or pits, which would cause cell lysis (18).

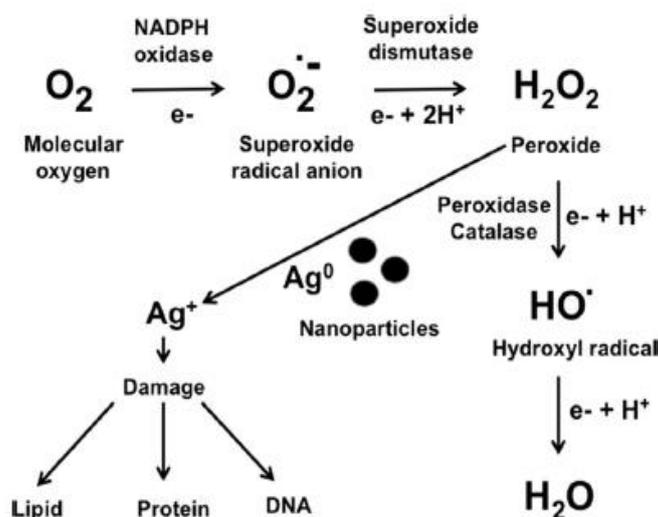


Fig. 2 shows a scheme outlining how NPs contribute to the production of ROS.(14).

3. Antibacterial Uses of Metal NPs

Researchers are interested in using metal nanoparticles (NPs) in a variety of medicinal applications as antibacterial agents due to the rise in bacteria that are drug-resistant. The versatility to change physical parameters to change the antibacterial properties of NPs, as well as their ease of manufacture, are only a few of their benefits. Implantable technology is one of the most popular applications for NPs. Implantable devices must have the necessary biocompatibility, tissue affinity, corrosion resistance, and most important of all, antibacterial capabilities [19].

Several metal and metal oxide nanoparticles (NPs) can now be added to implants to augment their antibacterial characteristics (20,21). AgNPs significantly reduced surface colonization and biofilm formation in PMMA-based bone cement, (22). While using hydroxyapatite- and silver-doped titanium nails during arthroplasty surgery, Kose *et. al.* saw equivalent results. They observed strong antibacterial activity, no prosthetic-related edema, and no evidence of the cytotoxic effect of the silver ions. Dental implants, catheters, and other medical devices have all demonstrated strong antibacterial properties. According to research, adding NPs to catheters could potentially stop the growth of biofilms and bacteria (23). In addition to creating an AgNP-coated collagen membrane for dental implants, showed that it was highly effective against *S. aureus* and *P. aeruginosa* while exhibiting low cytotoxicity. Adding copper and zinc oxide to dental plaque chalk significantly reduced the number of *streptococcus mutans* for 6 to 24 hours (24). NPs are frequently used in bandages for skin wounds as antibacterial components. Gram-positive and Gram-negative pathogenic bacteria can both cause long-lasting infections in skin wounds. AgNPs significantly reduced bacterial growth and accelerated wound healing when combined with poly (vinyl alcohol) and chitosan (25,26). The public's health is directly impacted by the work done by NPs in the agro-food sector, which includes, in particular, the food packaging sector, in identifying and eliminating diseases (27).



The degree to which NPs are antibacterial is greatly influenced by their surface charge. Negatively charged NPs are known to be more harmful than positive ones (39). Negatively charged bacterial cell walls interact electrostatically with other molecules. When compared to negatively charged magnetic NPs (NP), positively charged magnetic NPs (NP+) were found to successfully attract over 90% of *E. coli*, according to (40). Our results show that NP+ has strong electrostatic attraction and microorganism-trapping abilities. Abbaszadegan *et al.* examined the antibacterial efficacy of three distinct AgNP types—positively, negatively, and neutrally charged. They found that the level of bactericidal activity was highest for positively charged NPs and lowest for negatively charged NPs (42).

study 's focused on four AgNPs with a range of surface charges, from strongly negative to extremely positive. According to their study (43), AgNPs kill the tested bacterial species in a way that depends on surface charge. Ag-polyethyleneimine (BPEI) nanoparticles with a positive charge adhered to bacteria's surface more firmly than those with a negative charge, according to a different study. However, Agnihotri *et al.* discovered that *S. aureus* and *E. coli* growth was significantly inhibited by negatively charged AgNPs (stabilized by citrate). A smaller particle size was also found to enhance the antibacterial effect (44).

5. Nanoparticles and multidrug resistance (MDR)

Because they can lead to treatment failure, which can have devastating repercussions, especially in patients who are already extremely ill, MDR bacteria offer a serious danger to all areas of medical science (4). Through a variety of acquired or natural pathways, many microorganisms can evolve bacterial antibiotic resistance (45). The lack of a target or the existence of low-affinity targets, poor cell permeability, antibiotic inactivation, and the presence of efflux mechanisms are a few examples of intrinsic or "natural" resistance that exists in every bacterial species. The spread of resistance genes via mobile genetic materials like plasmids and antibiotic-targeted gene changes are two more methods I learned about. Transposons, bacteriophages, and other elements This exchange is typically carried out by transduction, conjugation, and transformation in bacteriophages, plasmids, and conjugative transposons (by integrating plasmids, additional DNA from extinct creatures, and chromosomal DNA into the chromosome). A few brand-new drugs have been developed in recent years to combat these MDR infections.

Nanoparticles have been found to cling to bacterial cell walls before entering, altering the structure of the membrane and ultimately causing cell death. In comparison to other salts, silver nanoparticles have a very large surface area, which allows for more contact with microbes and more potent antibacterial actions. The bacterial membrane may be targeted by SNPs, which would result in the proton motive force dissipating and stopping oxidative phosphorylation (46).

Another mechanism linked to microbicidal action is the generation of free radicals by nanoparticles, which have the capacity to harm and porosity the cell membrane and ultimately lead to cell death. Metal nanoparticles are drawn to DNA bases and other phosphorus and sulfur-containing parts of bacterial cells. These soft bases interact with the metal nanoparticles,



which can kill cells and damage DNA (47). According to **Singh et al.** , it has been proven that nanoparticles have an impact on bacterial signal transduction (6).

The dephosphorylation of peptide substrates on tyrosine residues by the nanoparticles inhibits bacterial growth and signal transmission. Moreover, it has been shown that silver ions from released Ag nanoparticles can attach to thiol groups on a variety of significant enzymes, inactivating them and impacting cellular processes. Also, by compressing the membrane potential, NPs can hinder the ATPase enzyme's capacity to lower the level of ATP or stop the ribosomal component from adhering to tRNA. A brief summary of some recent studies on the bactericidal abilities of various NPs and nanoconjugate systems is given in the preceding sections (48).

6. The Use of Nanosystems to Combat Antibiotic Resistance

Because there is a shortage of new antibacterial drugs and aggressive bacteria are on the rise, current antibiotic therapy is ineffective, which has detrimental effects on human health. The availability of novel antibacterial pharmaceuticals appears to be a highly challenging process that normally takes 10 to 15 years (6, 8). This is because it is possible to generate new antibacterial drugs. This is a result of the expensive production costs and drawn-out approval procedures for new medications. According to (48), many antibiotics completed clinical assessment in 2016 and were given the go-ahead to be sold in the United States.

Yet prior to recently, only the newly discovered antibiotic teixobactin and the drug linezolid had licenses (14). By improving the stability and physicochemical properties of antibiotics, facilitating biofilm internalization, extending antibiotic release, permitting targeted antibiotic administration to the site of infection, improving systemic circulation, and minimizing associated side effects, nanomedicine significantly contributes to increasing the efficacy of current therapeutics (14, 48).

7. Worldwide gene and protein modification following NP exposure

Its NPs have been demonstrated to alter the genomic and proteomic profiles of bacterial cells, indicating that the cells' capacity to adapt to their new environment has been enhanced by the presence of its NPs. For instance, it was shown that after exposure to Ag-NPs and Ag⁺, *E. coli* downregulated 27 genes and overexpressed a common set of 161 genes. It's interesting to note that 309 and 70 genes, respectively, were under the control of Ag-NPs and Ag⁺ alone (49). MgO-NPs in *Escherichia coli* differently regulated 109 proteins, with 83 of them being downregulated (50).

These proteins were mostly engaged in cellular processes like gene transcription and central metabolism. The increased genes were found in periplasmic proteins that bind thiamine and those involved in riboflavin metabolism, indicating that they might not be important for understanding MgO-NP exposure toxicity. Several ways may allow NP to affect the genes and proteins of bacteria.

7.1 DNA replication and repair effects of NP, paragraph



TiO₂-NPs prevented *Escherichia coli* from expressing two genes necessary for DNA replication [51]. It is likely that exposure to TiO₂-NP reduced DNA synthesis by downregulating the genes that produce *guaC*, *pyrC*, and *glutaredoxin (grxA)*. According to (20)., this shows that the cell is under stress and does not prioritize DNA synthesis (2015). According to (52)., several genes involved in amino acid transport (*argT*, *glnH*, *livK*, *tdtC*) and glutamine synthesis (*glnA*) are also upregulated (2015) This suggests that the cell is attempting to adapt to its environment. An intriguing gene called *RecA* is created after DNA damage and, when it is downregulated, it produces a phenotype that has been exposed to Ag⁺ [43]. It is unclear whether DNA repair is prevented by Ag⁺ directly inhibiting the gene or if other toxicity mechanisms are to blame *E. coli* cells exposed to Ag-NPs exhibited little to no overall change in their protein composition..., but distinct protein groups were controlled differently. The total protein-protein interactions in cells are not considerably changed by Ag-NPs' selective protein group binding [53].

7.2 The impact of NPs on proteins associated with sulfur

Genes involved in the metabolism of sulfur were found to be increased in bacterial cells exposed to NPs, suggesting that sulfur and NPs may be related. The majority of these genes are involved in sulfate metabolism, including those that reduce and assimilate intracellular sulfate during the synthesis of cysteine and sulfate/thiosulfate transporter elements of the ABC family. Each of these genes starts to work when exposed to Ag⁺. One of the primary causes of this upregulation may be the increased requirement for cysteine, an Ag⁺ target whose intracellular depletion initiates its production cycle (16). Only a few proteins have Fe-S clusters, including ferredoxins, hydrogenases, succinate-coenzyme Q reductase, bacterial respiratory complexes I–III, metalloproteins, and hydrogenases (17). The genes *iscX* and *hscB*, which are both involved in the formation of Fe-S clusters, were found to be significantly downregulated when TiO₂ was present in *E. coli* cells (54, 49), revealing that the Fe-S cluster encoding operons *isc* and *suf* are activated by Ag⁺.

7.3 ROS and gene regulation in metabolism

Among the proteins that have Fe-S clusters are ferredoxins, hydrogenases, succinate-coenzyme Q reductase, bacterial respiratory complexes I–III, metalloproteins, and hydrogenases (50). The genes *iscX* and *hscB*, which are both involved in the production of Fe-S clusters, were shown to be significantly downregulated when TiO₂ was present in *E. coli* cells (55). It has been discovered that Ag⁺ activates the operons *isc* and *suf*, which encode Fe-S clusters (50). Another gene that is activated by high levels of peroxide is *KatE*, a catalase that degrades H₂O₂ to protect cells from ROS damage. An AG-sensitive phenotype is created when the *katE* gene is deleted (43). As a result of exposure to Ag-NP, the expression of a different gene called *OxyR* has increased. In addition to being involved in peroxide metabolism and defense, this gene controls redox reactions. The *ADD*, *ASD*, *ADD C*, *KatG*, and other genes have also been linked to increased activity in these pathways. When these genes work together, an oxidative species is produced, which converts oxygen first into the potentially harmful H₂O₂ and then back into oxygen. After 90 minutes of exposure, the amount of *oxyR*



To address the major global public health concern of the evolution of bacterial resistance to antimicrobial drugs, novel antimicrobial therapies are urgently needed. As a consequence of innovative developments in nanotechnology, particularly nanoparticle engineering, new antibacterial agents should be created. Such nanoparticles have been created and tested for antibacterial activity by several research teams. Both gram-positive and gram-negative bacteria are impacted by anti-quorum sensing and antibiofilm activity. Nevertheless, NPs also have disadvantages, such as their small size, surface properties, and aggregation potential. Nanoparticle research is now one of the most studied areas in science since there are so many possible uses.

Nanoparticles (NPs) are a potent antibacterial alternative to antibiotics in the field of new antibacterial materials. These nanoparticles are efficient antibacterial agents against a variety of bacteria, including drug-resistant types, by concentrating on multimolecular biotic targets. A low dosage does not entirely eliminate germs while promoting the horizontal transfer of resistance genes and raising bacterial cell membrane permeability. At large doses, it could be lethal to eukaryotic cells. Due to their bactericidal properties, numerous metal (Ag, Zn, and Cu) and metal oxide (ZnO, CuO, MgO, and TiO₂) NPs have been extensively used in a variety of biomedical applications. Finally, standard NP production practices should be taken into account.

To increase the validity of these techniques in subsequent studies, cytotoxicity, and the inflammatory response must be taken into consideration.

Additionally, in order to address the rising prevalence of multidrug-resistant bacterial strains, clinical isolates rather than common microbial collection strains should be studied.

Acknowledgments:

This project was made possible thanks to the financial help of the College of Science, Babylon University, Hilla, Iraq.

Conflict of interests.

There are non-conflicts of interest.

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