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REVIEW ARTICLE

The Role of Nanoparticles in the Inhibition of Multidrug-Resistant Bacteria and Biofilms

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Abstract: ***Background***: Until recently, one of the main reasons for mortality has been infectious diseases, and bacteria that are drug-resistant have emerged as a result of the wide application, as well as the misuse of antibacterial medications. Having multidrug-resistance, bacteria present a great problem for the efficient management of bacterial infections and this challenge has resulted in the creation of other means of dealing with bacterial diseases. Of late, metallic nanoparticles (NPs), employed as antibacterial agents, have the potential for use against resistance to bacterial drugs.

Objective: The mechanisms of bacterial resistance are described in this review and this is followed by an outline of the features and uses of metallic NPs as antibiotic agents to address bacteria that are antibiotic-sensitive and resistant. Additionally, a general impression of metallic NPs as antibiofilm bactericidal agents is presented.

***Conclusion*:** Biofilms and bacterial strains that are resistant to antibiotics present a grave public health challenge and this has enhanced the need to develop new bactericidal agents. Therefore, nanomaterials are considered as a potential platform for managing bacterial infections.

Keywords: Nanoparticles, biofilm, selenium, bismuth, gold, antimicrobial activity.

1. INTRODUCTION

The wide application or misuse of antibacterial medications has resulted in the emergence of multidrug bacteria, which have risen to a remarkable level and are currently a grave matter of concern for medical practitioners dealing with contagious diseases. Resistance to antimicrobial therapy is quite complicated, and developmental procedures often take place during antibiotic treatment, resulting in the emergence of heritable resistance to antibiotics. Horizontal gene transfer (HGT), by means of transduction, transformation, bacterial conjugation or biofilm creation, may spread resistance to drugs [1]. In fact, resistance to drugs by bacteria has several harmful consequences for society and for medicine. Infection from drug-resistant bacteria requires the dispensing of raised doses of antibiotics, leading to raised drug toxicity, extended stays in hospital and increased mortality rates [2, 3]. In the United States, the cost of antibiotic-resistant diseases amounts to 20 billion dollars of the total healthcare budget and costs the population 35 billion dollars [3, 4]. Therefore, the efficient management or complete eradication of drug resistance is a significant objective in the battle against bacterial infections [5].

Both gram-negative and gram-positive bacteria are able to form biofilms on internal medical apparatus, including mechanical heart valves, prosthetic joints and catheters. The most widespread biofilm-creating bacteria related to human disease are *Enterococcus faecalis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus viridans*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Pseudomonas aeruginosa* [6]. Diseases related to biofilm are generally constant infections distinguished by slow progress [7]. Chronic infections are thought to be the result of a subpopulation of cells that have biofilms, referred to as 'persistent', which can endure long-term treatment with antibiotics and can then disconnect from mature biofilms, subsequently spreading to the systems of other organs [8]. The renowned resistance of biofilms to antibiotics could be the result of poor saturation of the antibiotic into the biofilm matrix, a different microenvironment and an adaptive bacterial reaction. Functioning in collaboration, these systems could increase the biofilms' antibiotic resistance by as much as 1,

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000 times, in contrast to free-living bacterial organisms [9]. The previously stated features of biofilms are considered to pose serious challenges. Therefore, great efforts are being made to find new technologies that could form the foundation for antibiofilm treatments and would be better than the current antibiotic methods of treatment [10].

Of late, NPs of metallic nature have been found to be flexible instruments that may be used for highly responsive analytical assessments, drug and gene delivery, radiotherapy and thermal ablation methods [11-13]. When applied as conveyers of medications, NPs could decrease the negative consequences and increase the healing effect of antibiotics by enhancing the pharmacokinetics and biodistribution [14]. Additionally, surface functionalized metal nano-architectures have been shown to have antimicrobial features and may, therefore, be employed in the management of infectious diseases [15, 16]. As distinct from customary antibacterial agents of organic nature, metal NPs have a raised ratio of area-to-volume of their surface, which improves distribution and conveys particular chemical, motorized, optical, electrical, electro-optical, magneto-optical and magnetic features to the NPs that differ from the features of their major characteristics [17]. The metal NPs antibacterial action is mainly reliant on volume and steadiness, as well as intensity within the growth medium [18]. Thus, in dealing with the bacterial resistance to medications, NPs demonstrate several abilities, such as an enhanced collection of antimicrobial instruments within the cells [19, 20] or prevention of the creation of biofilms [2, 21], and have fewer negative impacts compared with regular antibiotics [22]. The objective of this review is to consider the key mechanisms of biofilm resistance to traditional antibiotics and to detail the different techniques for treating or preventing biofilms, as well as discussing the action of metal nanoparticles (NPs) on antibiotic-sensitive and resistant microbes. In addition, an outline of metallic NPs as antibiofilm agents is presented.

2. MECHANISMS OF ANTIBIOTIC RESISTANCE

Multidrug resistance in bacteria appears to be caused by both the regulation of resistant genes and chromosomal mutations. Mechanisms of this type can be categorized into four groups (Fig. **1**).

2.1. Enzymatic Inhibition

Enzymatic inhibition occurs when antibiotic therapies are neutralized by bacteria before they can take action in the intended area. β-lactams, such as penicillin, have been well documented as having bacteria that develop this sort of resistance. β-lactam antibiotics are targeted at the transpeptidase enzymes, which cause the synthesis of cell walls by hydrolysing the amide bond of the four-member β-lactam circle [23-25]. In gram-negative bacteria, β-lactams are available within the periplasmic space, whereas gram-positive bacteria excrete β-lactamase [26]. β-lactamase genes are included in plasmids or transposons, resulting in the subsequent swift movement and conveyance of genetic materials to alternative bacteria. Additional changes to β-lactamase genes in these moving elements may result in systems for multidrug resistance that are made up of macrolides, sulphonamides, chloramphenicol and aminoglycosides [27].

2.2. Target Site Alteration

Target site alteration occurs when the target gene products of antibiotics are changed, avoiding the usual interaction between the bacteria and the antibiotics. Both 50S and 30S ribosomes are key targets for antibiotics [28]. Erythromycins (and alternative macrolide antibiotics) operate by binding to the 50S subunit and advancing the dissociation of peptidyl-tRNA from the ribosome, halting cell development and protein synthesis [29, 30]. 30S ribosome inhibitors, such as tetracycline, act by limiting the relation of aminoacyl-tRNA with the bacterial ribosome, disturbing protein synthesis [31, 30]. Such changes permit the bacterial cells to support homeostasis even though an antibiotic is present. Likewise, if a protein that is accountable for the synthesis of a growth element (which an auxotrophic bacteria may acquire from the environment) is targeted by an antibiotic, the antibiotic will be ineffective [32].

2.3. Alteration of a Metabolic Pathway

Sulphonamides are considered to be an example of the inhibition of dihydropteroate synthase in folic acid metabolism via a competitive mode with a higher affinity for the enzyme than for the substrate [33]. PABA, which is not required in some sulphonamide-resistant bacteria to perform folic acid, is an important precursor for the synthesis of folic acid and nucleic acid, therefore conferring sulphonamides with resistance [34]. Bacteria can inhibit the antibacterial activity of the antibiotic by enhancing the synthesis of a competitive molecule of PABA. In *S. aureus* or *N. meningitides*, sulphonamide resistance appears to be enhanced via increasing the PABA synthesis that diminishes the binding of drugs on dihydropteroate synthase and competes with sulphonamide molecules, thus resulting in sulphonamide resistance [35, 36].

2.4. Membrane Permeability Shifts

The exterior bacterial membrane is made up of lipopolysaccharides, phospholipids and transport proteins implanted within the membrane. Subject to regular conditions, hydrophobic antibiotics (aminoglycosides, macrolides, rifamycins, novobiocin, fusidic acid and cationic peptides) can penetrate the exterior membrane and enter the interior of the cell [37, 38]. Changing membrane penetrability involves altering the arrangement of the lipopolysaccharides' core oligosaccharide. The arrangement of the core oligosaccharide is highly variable, ranging between 6-10 monosaccharides. Bacterial strains have been observed to be resistant to hydrophobic antibiotics if the entire length of lipopolysaccharide is expressed [39, 37]. These resistant strains display a more tightly packed lipopolysaccharide level within their exterior membrane, limiting the penetration of hydrophobic antibiotics. The penetrability of the exterior membrane may additionally be altered by changing the porins entrenched within the membrane. Porin channels that are present in the exterior membrane allow minor, hydrophilic antibiotics, such as β-lactams, chloramphenicol, tetracycline and fluoroquinolones, to permeate the cell [37, 40]. Limiting movement across the porin channels reduces the efficiency of a particular antibiotic. Reduced membrane penetrability is usually followed by raised levels of antibiotic efflux [39, 41]. Drug efflux pumps

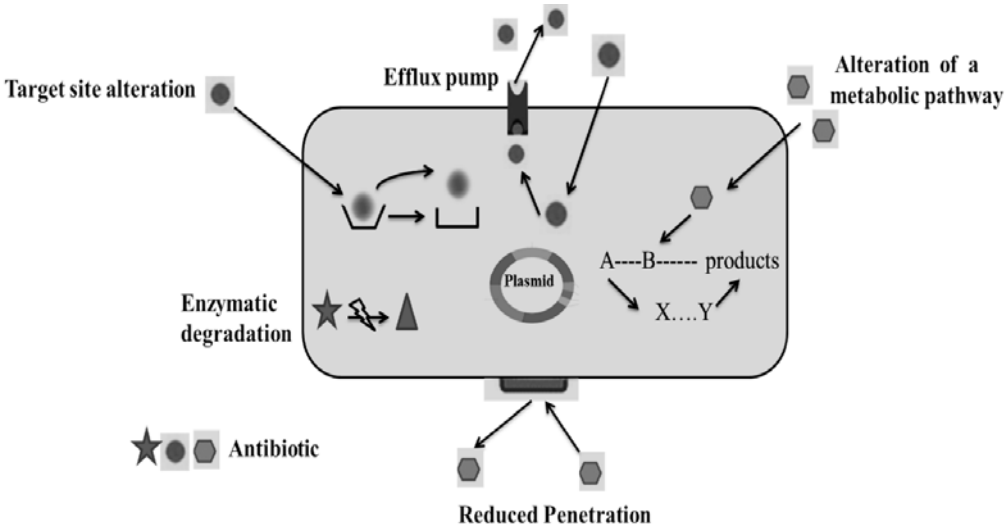

Fig. (1). Bacterial resistant strategies used against antibacterial agents.

contain loose substrate specificity, enabling them to interact with a great variety of drugs [42]. Although the exact mechanism for drug efflux is still contested, antibiotic efflux, in addition to reduced membrane penetrability, results in a sturdy resistance structure that could prove difficult to implement using standard therapy [39, 43].

3. CREATION OF BIOFILM AND MECHANISMS FOR ANTIBIOTIC RESISTANCE WITHIN BIOFILMS

A bacterial biofilm consists of a cooperative population of single-cell organisms linked either to a firm exterior or enclosed within a hydrated medium of protein and polysaccharide. As illustrated by Fig. (**2**), biofilms are normally created via a number of steps (Fig. **2A**). The first stage of biofilm creation comprises of bacteria clinging to a strange mass or biomaterial. The alteration from changeable to unchangeable connection is a reasonably swift procedure, occurring within several minutes or sooner [44, 45]. The bonding of bacteria is controlled by flagella, pili and fimbriae, as well as extracellular polymeric substances (EPS) that create a bridge of interaction that separates bacteria from the habituation films. As the biofilm develops, the collection and build-up of clinging bacteria result in the creation of several levels of cells. The final stage comprises disconnection into a planktonic condition of the bacteria from the biofilm, which permits these to commence a novel sequence of biofilm creation [46-48]. It has been shown that in biofilm cells, expression of the genes varies as compared to cells from plankton [49]. The control of genes is reliant on the number of cells, which is mediated by an indication molecule-compelled structure of communication, such as the quorum detection structure [50-53]. Quorum detection takes place within several various species and settings and is controlled by a range of elements, for example, Bacillus and Streptococcus generate and discharge virulence elements [54-58]. Biofilms can develop everywhere (for instance, on plants or on floor tiles) and in plants they can exist in a symbiotic relationship supported by the plant or they can result in infection of the crops. Additionally, a biofilm may develop on contact lenses as well as on biomedical implants [59]. Of late, the biofilm method of development was suggested to be the main element in persistent diseases. Biofilms may function as a nidus that generates regular planktonic bacterial sprays within the bloodstream, causing severe disease [60, 61]. Parsek and Singh (2003) [7] discovered that bacteria within biofilms demonstrate a thousand times increase in their resistance to antibiotics and are not as conspicuous to the immune structure [7]. Thus, using antibiotics to eradicate biofilm bacteria within the treatment centre is a challenge. The theory of medical opposition within biofilms, presented by Stewart *et al*. (Fig. **2B**) [62], is as follows. (1) Within biofilms, the permeation of antibiotics is gradual and incomplete. To effectively exterminate bacteria, diffusion and permeation of the bacterial cells by an antibacterial agent is required. Regrettably, EPSs influence the distribution of antimicrobial molecules by chemically responding to antibiotics or by restricting the extent of movement. Hoyle and colleagues stated that dispersed *P. aeruginosa* were fifteen times more receptive to tobramycin compared to undamaged biofilms [63]. Duguid *et al*. [64] illustrated that the receptiveness of *S. epidermis* to tobramycin could be reduced through biofilm creation [64]. (2) An intensity grade of a metabolic substrate or output, results in areas of gradually developing or non-developing bacteria having a reduced consumption of antimicrobial instruments compared to cells from plankton. Evans and colleagues stated that *E. coli* developed gradually in biofilms that were cetrimide resistant [65]. (3) Some bacteria express an adaptive stress reaction. To deal with environmental variations, such as a change in temperature, oxidative pressure and DNA damage, bacteria have developed reactions to stress that permit adaptation [66-69]. A number of stress reactions have been scrutinized in genetic and molecular detail within planktonic bacteria, and defensive stress reactions could be activated in biofilms. Benamara *et al*. [70] discovered that *E. coli* trapped within agar demonstrated superior resistance to aminoglycoside as oxygen pressures were reduced [70]. The proposal was made that obstruction by sessile-like bacteria towards aminoglycoside is the result of the reduced intake of antibiotics by bacteria with no oxy-

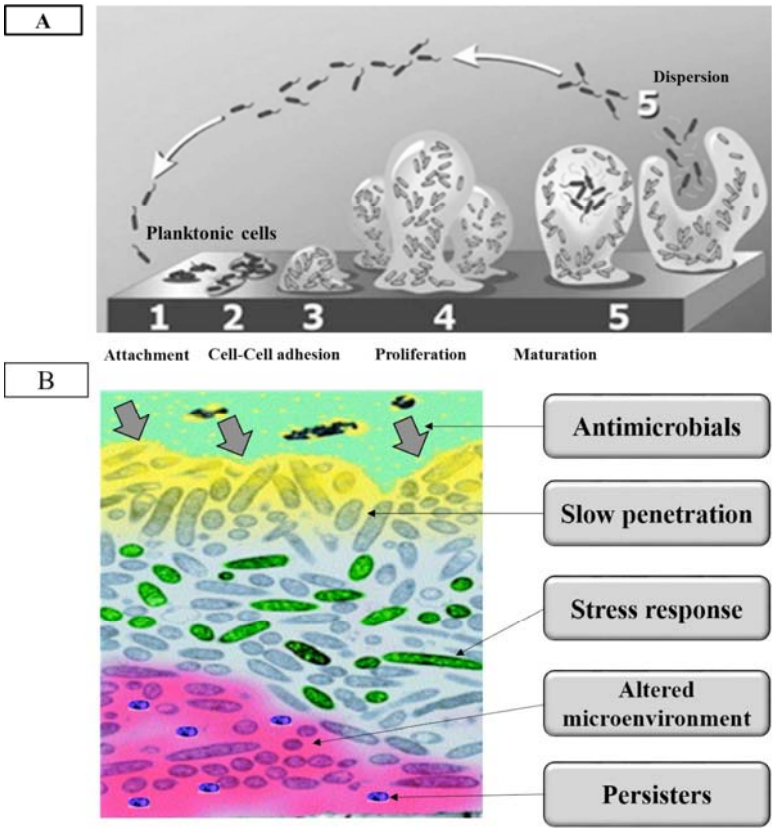

Fig. (2). The life cycle of biofilm with the antibiotic-resistant mechanism in biofilms.

gen provision [70, 71] (4) A small percentage of bacteria differentiate into a highly sheltered persister condition that decreases the receptiveness of the biofilm towards antibiotics. The persister theory may clarify the safety of biofilms from antimicrobial instruments of greatly varying chemistries and means of activity [72, 73].

4. NEW TACTICS TO ADDRESS BACTERIAL BIOFILMS

Compounds derived from plants could be viewed as new antimicrobials due to their considerable and verified antibacterial effects. Recent studies have described the biological action of secondary plant metabolites, such as polyphenols, which efficiently decrease biofilm creation through *Streptococcus mutans* [74, 75]. Another fascinating set of compounds are terpenoids; within this set, two pentacyclic triterpenoids, as well as their derivatives, are of particular importance. It has been illustrated that ursolic acid limits biofilm creation in a number of bacterial species and that alternative terpenoids demonstrate a strong antibiofilm activity towards staphylococci [76-78].

Recently, high-throughput screens have disclosed small compounds that have antibiofilm features. Small molecules can alter cell envelopes, quickly disassemble the extracellular matrix, or activate and commence the spread of biofilms [79, 80]. New bacterial biofilm creation inhibitors require additional scrutiny; nonetheless, they may be used as treatment agents, which may be viewed as options for antibiotics. Due to the significant function of cell-to-cell communication during the biofilm creation process, molecules capable of restricting this system are presently under scrutiny. It is proposed that quorum sensing (QS) inhibitors are efficient in managing biofilm-associated bacterial infections while not having any harmful impact on human cells [81, 82]. Remarkably, a number of molecules derived from plants can function as QS inhibitors. Examples of these include the compounds available in green tea extract, which adjust the QS related anti-virulent functions of *P. Aeruginosa* [83] or *ajoene*, a molecule from garlic that limits genes managed by QS from the same species of bacteria [84]. An alternative means of targeting biofilms is the application of synthetic cationic peptide variants taken from natural antimicrobial peptides. Alterations to synthetic peptides, through the involvement of cationic residues or changes in the quantity of hydrophobic residues, allow the modification of the antibiofilm and antiplanktonic action of these molecules. Such peptides, which can efficiently avert biofilm creation by gram-positive and gram-negative bacteria, have been detailed [85].

Antimicrobial photodynamic therapy (aPDT) concerns the application of a mixture of dye and visible light of a low intensity that, in the presence of oxygen, generate cytotoxic reactive oxygen species. It has been illustrated that numerous biofilms are receptive to aPDT, especially for dental diseases [86, 87].

Current reports illustrate that recently designed biomaterials could limit biofilm creation by obstructing bacterial attachment. Thus, these recent methods involve the design of new mechanisms with surfaces that are able to restrict bacte-

rial attachment or viability [88, 89]. Most of the novel nanotechnological methods used to address biofilm creation are founded on the use of NPs to functionalize the exterior of biomaterials through coating [90-92], impregnation [93], or by implanting nanomaterials [94].

5. ANTIBIOFILM ACTIVITY OF NANOPARTICLES

Metal NPs are made up of collections of atoms and range in size from 1 to 100 nm. These compounds vary from colloids made up of NPs, in addition to some particles ranging in size from 100 to 2, 500 nm [95, 96]. A number of metals, including zinc and silver, are renowned for their natural antibacterial activity. It has been established that in nano sizes, the biological features of metals are stronger, causing NPs to be fascinating from a medical perspective [97].

The antibacterial function of all the NP varieties is not completely known. It has previously been stated that none of the activity is the result of the raised surface-to-volume ratio. The surface area of a dose of NPs is raised as the size of the particle is reduced, thus permitting a greater material interaction with the immediate surroundings [98, 99]. Small NPs seem to be the most able to permeate bacterial cells. In addition to the particle size, their form, zeta potential and chemistry are some of the most pertinent elements influencing antibacterial activity. A highly positive zeta potential for an NP encourages NPs' interactions with the membranes of the cells, membrane disturbance, bacteria flocculation and a decrease in viability. It has therefore been suggested that zeta potential, in addition to particle size and chemistry, are highly significant parameters accountable for antimicrobial impacts [98, 99].

6. ANTIMICROBIAL ACTIVITIES OF NANOPARTICLES

Nanoparticles have been viewed as some of the most capable bioactive agents, mostly due to their great surface-area-to-volume ratio [100, 101]. Nano-powders have antimicrobial features that act against different fungal, bacterial and viral human pathogens [102, 103] (and can swiftly kill bacterial cells [90% in 1 hour (h)]). The antibacterial features of titanium dioxide and silver nanoparticles have been considered as coatings for surgical masks [104], as well as for a number of other clinical applications. The nanoparticles that have been observed to have antimicrobial results are silver [105, 106], titanium dioxide [104], fullerenes [103], zinc oxide [107] and magnesium fluoride [108]. The antibacterial operation of fullerenes has been documented in response to *Escherichia coli*, *Salmonella* and *Streptococcus* spp. [103]. The capacity of zinc oxide nanoparticles to disrupt the membrane penetrability of *E. coli* has also been identified [18]. The broad-ranging antimicrobial function of silver nanoparticles has been credited to their ability to destabilize the exterior membrane of the bacteria and to exhaust adenosine triphosphate (the main form of energy) within bacteria [105, 106]. Green synthesized AgNPs (18 nm) demonstrated the bactericidal activity in relation to *E. coli* and *P. aeruginosa* by using the agar well diffusion approach [109]. AgCl NPs have been produced either via the reduction of Ag+ (AgNO3) using an aqueous leaf extract of *S. altissima* or via the photoreduction of AgCl NPs. These particles have demonstrated antibacterial activities [110]. Small and uniform AgNPs (7 nm) have been synthesized through a biosynthesis reaction using *Chlorella vulgaris* secretory carbohydrates. AgNPs have been found to demonstrate antimicrobial activity towards *S. aureus* and *E. coli* with MIC 37 μg ml^{-1} and 9.4 μg ml^{-1}, respectively [111]. Spherically shaped silver nanoparticles, with particle sizes of 65.92 and 64.64 nm, have been synthesized from the *Penicillium* species. The growth of *E. coli* and *P. aeruginosa* were strongly blocked by PsAgNPs at maximum levels [112]. Engineered silver nanoparticles (10-15 nm) have been synthesized with silver nitrate salt acting as the precursor. The inhibition efficiency against bloom-forming cyanobacterial *M. aeruginosa* ranged from 18.2% at 0.005 mg l^{-1} of AgNPs to 98.7% at 1 mg l^{-1} of AgNPs [113]. Additionally, fullerenes have been demonstrated to have neuroprotective and anti-apoptic, as well as anti-HIV functions [103]. The size-reliant interactions of silver nanoparticles, as well as the HIV-1 virus, which cause the restriction of host-viral interactions, have been identified [109]. The possible antibacterial uses of selenium NPs, bismuth NPs and gold NPs are detailed below.

6.1. Selenium-Based Nanoparticles

Selenium was discovered in 1817 by Jöns Jacob Berzelius, a Swedish scientist and one of the pioneers of contemporary chemistry, who named it *Selene* after the Greek word for moon [110]. Selenium is noxious for prokaryotes such as algae or bacteria, although extended constant exposure to selenium results in the creation of selenium resistant strains [111]. Selenium resistance is subject to the capacity for reduction from selenate or selenite to selenide [112]. The precise system of selenium noxiousness is vague, although there are numerous data regarding its prooxidant impact, especially in the form of selenite [113-117], whereas selenocysteine and selenomethionine are not as poisonous [118]. The prooxidant operation of selenium can also account for cellular apoptosis and could result in a practical pharmaceutical use for selenium compounds as antibacterial and antiviral, as well as antifungal, agents [118, 119]. Due to their outstanding anticancer function and reduced toxicity, selenium nanomaterials, such as nanoparticles, nanorods and nanowires, as well as nanotubes, have been widely explored and employed in a number of areas [120-122]. In one study, selenium nanoparticles (SeNPs) underwent biosynthesis through dispensing 1mM SeO2 into the free-cell supernatant of *Bacillus licheniformis* separated from food remains. The biogenic SeNPs (1-50 nm) demonstrated an antimicrobial impact towards six pathogens found in food: *B. cereus*, *E. faecalis*, *S. aureus*, *E. coli* O157:H7, *S. typhimurium* and *S. enteritidis* [123]. Another research study examined Se0-based nanoparticles bio-synthesized with *Stenotrophomonas maltophilia* SeITE02. Se0 nanoparticles have antimicrobial eradication properties towards *E. coli* JM109 and *P. aeruginosa* PAO1, as well as *S. aureus* ATCC 25923 [124]. Reports published in the literature credit the antibacterial impact of various selenium mixtures on the creation of open radicals [125]. Furthermore, selenium oxyanions have also

been observed to promote the production of reactive oxygen species (ROS), with the two being able to react to thiols within the cells and creating intermediates that result in oxidative pressure as an outcome of the creation of superoxide radicals [126]. Therefore, although reactive oxygen species are part of the danger of NPs, there have to be alternative systems that are accountable for the antimicrobial operation of such nanostructured metals. An example is that nanoparticles may play a role in the functional impairment of the cell wall or membrane by disturbing the integrity of these crucial envelopes [127]. A further mechanism associated with the exterior characteristics of nanoparticles is concerned with conveying noxiousness to NPs [128]. A synergistic nanocomposite has been synthesized through the application of quercetin (Qu), as well as acetylcholine (Ach), to the exterior of Se nanoparticles (Qu-Ach@SeNPs). Incubation of bacteria using nanoparticles with an intensity of 25.0 μg /mL for 10-60 min was undertaken. It has been illustrated that, with the exception of Qu@SeNPs, all nanocomposites considerably minimize the viability of *E. coli* and *S. aureus* cells over time. When *E. coli* and *S. aureus* were treated with Ach@SeNPs and Qu-Ach@SeNPs for one hour, Ach@SeNPs decreased the feasibility of the two bacterial classes by 60%. Qu-Ach@SeNPs decreased the feasibility of *E. coli* and *S. aureus* cells by 91.7% and 92.3%, respectively. Such outcomes illustrate the high antibacterial application of Qu-Ach@SeNPs and additionally verify that Qu-Ach@SeNPs demonstrates a synergistically improved antibacterial functioning towards the superbugs that resist several drugs (MDRs). These results imply that the synergistic features of quercetin and acetylcholine improve the antibacterial action of SeNPs. In this respect, Qu-Ach@ SeNPs make up a novel class of inorganic nano-antibacterial instruments that may be used for practical applications within biomedical strategies [129]. Bactericidal antibiotics encourage the production of ROS to eliminate bacteria [130]. It has been stated that due to their action as oxidase mimics, V2 O5 NPs restrict bacterial biofilms by means of ROS [131]. It is therefore possible that the antibacterial operation of Qu-Ach@SeNPs is connected with the production of reactive oxygen species within bacteria. Furthermore, another study has outlined the varying antimicrobial features of nanoparticles of selenium towards *S. aureus* and *E. coli*. Significantly, it was plainly shown by bacterial assays that the development of *S. aureus* was restricted by the nanoparticles (30 to 70 nm) at intensities as low as 1 ppm. The development and feasibility of *E. coli* was not influenced during any of the appraised concentrations [132]. It is possible that in the case of *E. coli* there was a considerable electrostatic rejection between the SeNPs and the exterior bacterial membrane, which consists of a net negative charge as a result of the lipopolysaccharide and covering. However, this does not apply to *S. aureus*. Within gram-positive bacteria, the remaining surface charge is significantly less negative compared to gram-negative bacteria [133, 134]. Indeed, if the *S. aureus* surface has a strong but negative net charge, they would subsequently be unable to adhere to glass or polystyrene and create biofilms [134]. A nonaligned or slightly positive charge is therefore preferable for hostility. The surface of *S. aureus* is peptidoglycan and is comprised of a -3 to +1net charge subject to environmental pH, as well as the development conditions for bacteria [135, 136]. Therefore, the electrostatic contact could essentially place SeNPs within the peptidoglycan level of *S. aureus* and halt the splitting of bacterial cells, thus conforming to the observation that SeNPs restricted the growth of *S. aureus* [132]. A comparison of the impacts of silver phosphate (SPNPs) and selenium nanoparticles (SeNPs) on the development of *S. aureus* has been undertaken. This has disclosed that at an intensity of 300 μ M, SPNPs (200-300 nm) resulted in a 37.5% limiting of bacterial development and SeNPs (50-100 nm) completely halted bacterial development. The availability of nanoparticles reduced the thawing temperatures for nanoparticle combinations of the zntR gene by 23% in the case of SeNPs and 12% for SPNPs, in contrast to the control. The intensity of bacterial metallothionein was reduced by 87% following the use of SPNPs, but was increased by 29% following application of SeNPs, in contrast to the *S. aureus* control. The interaction between DNA and SeNPs, in which these particles possibly damage the DNA arrangement of the zntR gene, was increased *in vitro* [137]. Beheshti *et al*. [138] stated that SeNPs might limit the dispersion of *Leishmania major* in promastigote and amastigote states. Apoptosis was demonstrated by DNA disintegration within the intensity **score** of 1-150 μg mL-1 of SeNPs [138]. A comparable noxiousness result of SeNPs for genomic DNA was found by Chen *et al*. [139] in the case of human melanoma cells administered with chemically synthesized SeNPs. Therapy for A375 human melanoma cells using SeNPs caused dosage-reliant cell apoptosis, as illustrated by DNA disintegration and phosphatidyl-serine transposition [139]. Holinka *et al*. [140] examined whether covering titanium discs in selenium in the form of sodium selenite reduced the bacterial attachment of *S. aureus* and *S. epidermidis* and obstructed osteoblastic cell development. The assessed strain of *S. aureus* demonstrated a greatly reduced attachment to the titanium discs, at 0.5% and 0.2% selenium coating. In addition, *S. epidermidis* demonstrated a highly significant decrease in bacterial attachment to discs covered in 0.5% and 0.2% selenium solutions. No obstructive effect of the selenium coating was observed on the osteoblastic cell development [140]. Inorganic antimicrobial agents present an attractive option to antibiotics due to their reduced danger of drug resistance, superior antibacterial capability, excellent biocompatibility and satisfactory stability. The additive most commonly used is silver [141, 142], regardless of its known cytotoxicity to fibroblasts [143] and the increased expense in clinical application. Ramos and Webster illustrated that selenium had a constructive influence on the development of fibroblasts and could therefore be considered as a potential option [144]. Kumar *et al*. [145] demonstrated the superior antibacterial consequence of sodium selenite on *Helicobacter pylori*, as well as its therapeutic effect on ulcers [145]. Matthews *et al*. [146] found a reduction in the bacterial colonisation of rabbit cornea in contact lenses covered in selenium, as well as satisfactory tolerability and no damage to the wellbeing of the cornea [146]. Thus, covering medical instruments in sodium selenite could have potential as an efficient technique for avoiding nosocomial implant-related infections, with no risk of developing antibiotic resistance or cytotoxic consequences [140].

Tran *et al*. [125] illustrated the efficiency of a 0.2% selenium covering on cellulose wound dressings on *P. aeruginosa* and *S. aureus*. Yang *et al*. [147] have noted the antagonistic effects of selenium-enriched probiotics on pathogenic *E. coli*. Several of the new organoselenium compounds are additionally renowned to have practical applications against a number of bacterial species, such as *S. aureus, S. simulans, Salmonella typhimurium, E. coli* and *B. cereus* [148, 149].

6.2. Bismuth-Based Nanoparticles

Bismuth comprises a crystalline, brittle metal and is made of the most natural diamagnetic metal. Generally, bismuth originates as bismuthinite, bismite and bismuthite [150]. Bismuth has the feature of expanding as it freezes and also has abnormally high electrical resistance to metal. Its thermal conductivity is below that of any metal other than mercury [151]. Bismuth oxide is a derivative of considerable technological significance and is used in the production of glass and ceramic items, as well as being a catalyst for the oxidation of hydrocarbons. It is widely employed in microelectronics and sensor technology, as well as optical technology [152, 153]. Colloidal chemistry offers the opportunity to produce uncomplicated synthetic routes to acquire bismuth nanoparticles with well-managed size distributions and raised crystallinity [154-163]. Overall, commercial bismuth salts are employed as precursors and, in addition, surface modifier species and a minimising agent are included to generate the nanoparticles [164].

A structural description of the NPs is acquired through X-ray diffraction evaluations of the bismuth colloids and HR-TEM [164]. This synthesis technique is the most broadly employed to acquire metal nanoparticles; it is cost-efficient and scalable to industrial production. This is a significant feature for their use with humans. Bismuth compounds are most broadly employed in the treatment of gastrointestinal disorders. Even though elemental bismuth demonstrates antimicrobial activity, it only achieves this at comparatively high intensities as a result of its restricted water solubility. Nonetheless, solubility is raised following chelation and bismuth's antimicrobial features are demonstrated at considerably reduced (order of micromolar) intensities, with bismuth dimercaptopropanol (BisBAL) being highly efficient against a number of bacteria [26]. Nonetheless, the long-term efficacy of BisBAL could be restricted as it is readily consumed on contact with microorganisms. This is the reason for our scrutiny of BisBAL in its nanoparticulate state and we adopt the view that its gradual dissolution would permit it to function as an antimicrobial agent over a longer period [27]. Bismuth compounds are significant elements in stomach remedies, for example, Pepto-Bismol (bismuth subsalicylate, BSS) [28]. De-Nol (colloidal bismuth subsalicylate, CBS) and by-products from CBS, such as ranitidine bismuth citrate (RBC), are presently undergoing improvement [22]. The variety of bismuth compounds in medicine goes as far as syphilis treatment [29] and tumours [30], as well as radioisotope treatments [31]. Of late, bismuth nanoparticles have been applied in biomolecules diagnosis, in addition to a broad spectrum of antimicrobial agents [37-42]. It has been stated that bismuth nanoparticles (Bis-NPs) may restrict bacterial development at intensities below 1mM [32]. When combined with X-ray treatment, nanoparticles containing bismuth have additional potential in the treatment of drug-resistant bacteria [44]. As X-rays may easily permeate human tissues, this bactericidal method has the potential for use in efficiently killing deeply embedded MDR bacteria. It has recently been reported that Bis-NPs restricted the development of *Helicobacter pylori*, changing their Krebs cycling, amino acid and nucleotide metabolism [45].

In brief, Bis-NPs offer antiviral fungicidal and bactericidal activity. On the basis of bismuth subsalicylate application in the treatment of stomach illnesses, it has been theorized that Bis-NPs are not noxious to human cells, to the point where we anticipate no reports signifying secondary consequences from bismuth nanoparticles. No cytotoxic influence was observed following the exposure of monkey kidney cells for 24 h at a final intensity of 2mM of Bis-NPs [37]. Bismuth nanoparticles comprise a potential method of combating infectious diseases, although additional testing is necessary to ascertain their safe application for humans. Significant antimicrobial activity is demonstrated by silver nanoparticles, although a number of reports suggest that they could produce significant toxic consequences [16, 17, 6]. A study of the genotoxic consequences of bismuth (III) oxide nanoparticles (BONPs) with regard to the root cells of *Allium cepa* by Allium and Comet assay, found that BONPs display genotoxic action in *A. cepa* root meristematic cells [47].

6.3. Gold-Based Nanoparticles

During the 1920s Robert Koch noted the bacteriostatic consequences of gold cyanide and applied it to the treatment of tubercle bacillus [83]. Gold combinations are clinically employed in the treatment of numerous diseases, such as rheumatic diseases, juvenile arthritis, discoid lupus erythematosus and palindromic rheumatism [84]. Gold NPs may disclose intense assimilation of light within the perceptible area as a result of the coherent vibrations of the open electrons on the exteriors of the particles. This occurrence of surface plasmon resonance (SPR) within gold NPs currently has different uses [85]. For instance, SPRs stimulated optically through the improved whole reflection may be employed as biosensors [86, 87]. Furthermore, gold NPs consisting of coherent vibrations boundary states and interband electronic transitions (d to sp) [88] display optical features and photothermal impact for the destruction of tissues and cells [89]. Even though gold NPs on their own are viewed as not having any antibacterial activity, Vidya *et al*. [165] synthesized functionalized AuNPs (FAuNPs), a process that was carried out using third generation antibiotics (levofloxacin, ceftriaxone and cefotaxime) and, as a second generation antibiotic, ciprofloxacin comprising a diameter of about 20-30 nm. Compared to free antibiotics, FAuNPs demonstrated superior inhibitor action in opposing gram-negative bacteria, *K. pneumonia* and *E. coli*, and gram-positive *S. aureus* [165]. The functionalization of amoxicillin on gold nanoparticles (GNPs) has been examined. The GNP-Amox conjugates illustrate improved bactericidal broad-spectrum activity towards bacteria that was gram-positive and gram-negative. Additionally, *in-vitro* assay of GNP-Amox disclosed string

anti-MRSA action and improved the survival rate [166]. The reversion and improved efficiency of amoxicillin combined with GNPs could be a result of the rise in the intensity of antibiotics in the area of bacterium-antibiotic interaction, enabling binding of the antibiotics to the bacteria and obstruction of the bacterial efflux pump in the extraction of GNP-AMOX [167]. Thus, this research demonstrates the positive features of a GNP-Amox conjugate as a potential antibacterial therapeutic agent for MRSA and other pathogens [166]. Gold and silver nanoparticles (Au- and Ag-NPs) were biosynthesized using the gum extract of *Prunus armeniaca*. Au- and Ag-NPs (5-40 nm) had remarkable antibacterial activity against *S. aureus E. coli* and *P. aeruginosa* [168]. Due to no antibacterial action being present in the gum extract, it may be said that the bactericidal action could be a result of the synergistic action of gum stabilized Au- and Ag-NPs and unreduced Au (III) or Ag^{+} ions [166].

Gold nanoparticles were synthesized using *P. fluorescens* 417 inhabiting *Coffea arabica L*. The research disclosed the bactericidal action of synthesized nanoparticles (5 nm to 50 nm) against a group of clinically important pathogens. The maximum action was noted towards *P. aeroginosa* and this was followed, in order of intensity, by *E. coli*, *S. aureus*, *B. subtilis* and *K. pneumoniae*. The findings show potential for eco-friendly methods for the synthesis of gold nanoparticles with bactericidal action that may function as an option for the fight against drug-resistant pathogens [169]. Bio-inspired eco-friendly gold nanoparticles were synthesized using a green technique and employing *Plumeria alba* aqueous flower extract (PAFE). The application of 1% and 5% intensities of PAFE resulted in two varying sizes of *P. alba* gold nanoparticles: PAGNPs1 (28 ± 5.6 nm) and PAGNPs2 (15.6 ± 3.4 nm). The antibacterial actions of PAGNPs1 and PAGNPs2 were assessed against *E. coli*. All PAGNPs1 and PAGNPs2 displayed antibacterial action against *E. coli*. Furthermore, the small-sized PAGNPs2 displayed superior antibacterial action. All PAGNPs1 and PAGNPs2 samples created disruption to the development cycle of bacteria by disturbing the log phase and causing a decrease in the number of viable cells [170]. This growth restrictive consequence was seen more clearly in PAGNPs2, which additionally verifies the conclusion that smaller particles display superior antibacterial potential, possibly due to their greater surface area available for interaction, in contrast to that of larger particles [171]. Biosynthesized gold nanoparticles employing *Dracocephalum kotschyi* leaf extract (d-GNPs) were observed to display no action against *S. aureus*, *P. aeruginosa*, *B. subtilis*, *B. cereus*, *E. coli*, *Ps. aeruginosa* and *Proteus vulgaris* [172]. Nonetheless, various sizes of gold nanoparticles (GNPs) using the dried fruit extract of *Tribulus terrestris* have been explored in respect of *Helicobacter pylori*. Anisotropic GNPs comprising average sizes of 7 nm and 55 nm were synthesized in ambient circumstances. GNP7 and GNP55 both displayed anti-*Helicobacter pylori* action against multidrug resistant clinical strains of *H. pylori* [173]. This could be a result of the physicochemical features of NPs that have a significant function in the tolerance or receptiveness of bacteria with NPs available [174]. A synthesis of essential oil of *Nigella sativa*-based gold nanoparticles (NsEO-AuNPs) was undertaken. The antibacterial action of NsEO-AuNPs (15.6 and 28.4 nm) was more significant against gram-positive *S. aureus* than gram-negative *Vibrio harveyi* [175]. Geethalakshmi and Sarada [176] found that gold nanoparticles synthesized from *Trianthema decandra* displayed exceptional action against *Yersinia enterocolitica*, *Proteus vulgaris*, *E. coli*, *S. aureus* and *S. faecalis* [176].

Park *et al*. [177] concentrated on the arrangement of resveratrol nanocarrier structures and the appraisal of their *in vitro* antibacterial functions. Green synthetic routes were employed to synthesize gold nanoparticles (AuNPs) for resveratrol nanocarrier structures. The mean magnitude of the nanoparticles varied between 8.32 and 21. 84 nm. Overall, with regard to bacteria that was gram-positive and gram-negative, the Res-AuNPs displayed additional antibacterial activity in contrast to the resveratrol alone. Among the appraised variations, the greatest antibacterial operation of the Res-AuNPs was noted for *Streptococcus pneumonia* [177]. Gold nanoparticles were synthesized employing a cell-free supernatant of *Pseudomonas veronii*, a novel endophyte separated from *Annona squamosa L*. Biosynthesized gold nanoparticles (5 to 25 nm) were more susceptible to gram-positive *S. aureus* when contrasted with gram-negative bacteria, *E. coli*. Furthermore, an unharmed band using control DNA was revealed in the electrophoresis gel in the absence of gold nanoparticles. However, DNA treated with nanoparticles displayed impaired and deformed DNA with a lightly coloured band, signifying the operation of nanoparticles on DNA [178]. Areca catechu nut has been employed in the synthesis of gold nanoparticles. The antibacterial action of synthesized GNPS has been scrutinized on various bacteria using the agar well diffusion technique. GNS (13.7nm) illustrated antibacterial action towards various human pathogens: *E. coli*, *K. pneumonia*, *P. auroginosa*, *Enterobacter sp*. and *S. aureus*. Therefore, the biogenic GNPS with antibacterial action would find uses in biomedical disciplines [179]. The antimicrobial action of AuNPs, arranged using the plant extracts of *Carica papaya* and *Catharanthus roseus*, was appraised in respect of the pathogenic bacteria *S. aureus*, *E. coli*, *B. subtilis* and *P. vulgaris*. The outcomes clearly illustrate that the AuNPs were more active towards gram-negative bacterial strains than to the gram-positive strains employed in this study [180]. An easy and swift imitation technique for gold nanoparticles (AuNPs) was established employing parts of *Inonotus obliquus*. The AuNPs were spherical, triangle, hexagonal and rod-like in shape with an average diameter of 23 nm. The antibacterial action of the AuNPs was scrutinized against gram-positive *B. substilis* and *S. aureus* and gram-negative *E. coli*. The greatest antibacterial action was noted towards *S. aureus*, followed, in turn, by *E. coli* and *B. substilis* [181]. The specific mechanisms that permit gold NPs to restrict bacteria development are currently subject to scrutiny. Cui *et al*. [182] discovered that the antibacterial activity of gold NPs is reliant on two occurrences: (1) reducing the ATP extents within cells through the replacement of membrane feasibility, or (2) the limitation of ATP synthase action and the limitation of the tRNA-binding subunit within the ribosome. The activity of gold NPs excludes ROS systems, even though ROS impairment is the

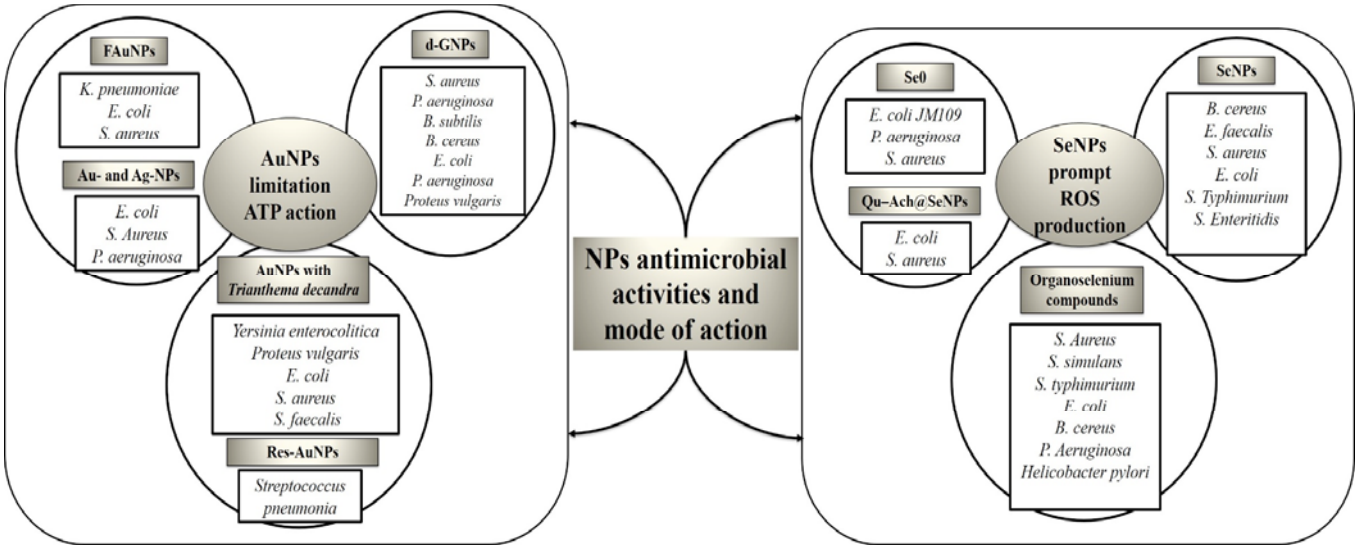

Fig. (3). The impact of NPs on bacterial cell survival.

reason for the death of cells caused by several nanomaterials and bactericidal antibiotics [182]. Fig. (**3**) illustrates the antimicrobial activities of NPs with their mode of action.

7. TOXICITY OF NANOPARTICLES

There remain a number of drawbacks of antibacterial agents in the form of metallic NPs. The primary issue is related to the possible nanotoxicity of metallic NPs following treatment. To enable the application of metallic NPs as antibacterial instruments for the wellbeing of humans, the toxicity of exposure of NP in humans and animals has to be scrutinised prior to large-scale production [183]. The noxious levels of NPs are influenced by three elements. (1) The solubility, charge and form of the NPs result in varying extents of noxiousness within animals [184]. (2) The alteration of NPs or their exteriors may additionally adjust their noxiousness. For instance, morphological alterations of nanomaterials could result in them being unrecognisable to phagocytic cells, resulting in additional toxicity [185]. (3) The magnitude of NPs also impacts their toxicity. Minor NPs that demonstrate effective antibacterial action could easily infiltrate the skin, brain and lungs, resulting in negative consequences. Furthermore, treatment with metallic NPs could result in their accumulation mostly within the organs, such as the kidney, spleen and liver, causing various levels of injury [186]. To methodically decipher the nanotoxicology of NPs, the Nanotoxicological Society has produced overall directions and instituted general regulations concerning nanotoxicology for additional nano-associated research that may effectively increase the use of nanoproducts in clinical settings [187].

CONCLUSIONS AND FUTURE DIRECTIONS

Biofilms and bacterial strains resistant to the antibiotics that are currently in use have become a grave public health challenge that has raised the requirement to develop new bactericidal materials. As a result, there is a strong requirement to establish new tactics and new materials that can address these serious challenges. The emergence of nanotechnology has resulted in numerous new antimicrobial alternatives. The small magnitude of the NPs is appropriate for the performance of antimicrobial activities. Organic, metal and other types of nanoparticles have demonstrated great potential as fungicidal and bactericidal elements, displaying their potential as effective antibiotic reagents in associated medical matters. The effectiveness of these nanoparticles differs according to their features, which include shape, size and intensity. Furthermore, the atomic profusion on the exterior of the particles has a considerable function in the features of these materials. As the magnitude of the particles is reduced, the proportion of atoms on the surface is increased comparative to the total atoms of the material, thus augmenting the action. Different NPs show antimicrobial action towards many species of pathogenic viruses and bacteria. At present, nanomaterials are a potential platform for a range of methods for managing bacterial infections. Table **1** the effect of different metallic NPs on pathogenic bacteria together with their biofilm. However, additional studies are required and these include the following. (1) An understanding of the electrostatic interaction between the SeNPs and the bacteria and the function (if any) of PVA (Penicillin amidase) in the interaction between bacteria and SeNP is required. (2) Selenium's *in vivo* biocompatibility and antimicrobial action needs to be clarified. (3) Additional scrutiny of animal models needs to be undertaken to guarantee the optimal bactericidal action and biodistribution, as well as the reduced host toxicity in (AuNPs). (4) The molecular mechanisms of biofilm-restrictive influence on SeNPs and alternative Se compounds have not yet been entirely understood and require additional research. (5) With regard to BisBAL NPs, there should be research into a possible future application that considers their inclusion in a buccal antiseptic for the prevention of oral infections. (6) Additional studies on the likely cytotoxicity of bismuth nanoparticles are necessary to trace any secondary influence in humans. (7) The possible dangers and toxicities of metallic NPs require scrutiny by means of systemic and consistency appraisal techniques.

Table 1. Showed different metallic NPs against pathogenic bacteria with their biofilm

Metal NPs/size	Bacteria	Antibiotic Resistance Type	Antibiofilm dosage	Main Results	References
Se NPs (80-220 nm)	*S. aureus*, *P. aeruginosa*, and *P. mirabilis*	Biofilm creation	(0–16 g mL^{-1})	Restricted the biofilm of *S. aureus*, *P. aeruginosa*, and *P. mirabilis* by 42%, 34.3%, and 53.4%, correspondingly.	[184]
SeNPs (10–50 nm)	*B. cereus*, *Enterococcus faecalis*, *S. aureus*, *E. coli*, *S. Typhimurium*, and *S. Enteritidis*	Biofilm creation	(20 µg/mL)	Have antibiofilm impact of all tested strains apart from *B. cereus*. Additionally, the concentration of 75 µg/mL displayed minor effect on extracting the established biofilm for all scrutinised bacteria.	[119]
SeNPs (221.1 nm-357.1 nm)	*E.coli* JM109, *P. aeruginosa* PAO1, and *S. aureus* ATCC 25923	Biofilm creation	(60 mg/L)	SeNPs completely removed the biofilm structure of *E. coli*. At similar concentration (60 mg/L), SeNPs killed the majority of biofilms cells for both *P. aeruginosa* and *S. Aureus*	[120]
SeNPs with ATBs (ampicillin, oxacillin and penicillin).	*S. aureus* and MRSA	Biofilm creation	ATBs (100 µM) + (100 µM) SeNPs	The biofilm arrangement was strongly restricted (up to 99% ± 7% for *S. aureus* and up to 94% ± 4% for MRSA) following application of SeNPs	[185]
Se NPs (50 nm)	*S. aureus*	Biofilm creation	69.00 g/m^2	The success of Bacteria biofilm restriction reached about 90%.	[186]
*Ns*EO-AuNPs (15.6 - 28.4 nm)	*S. aureus* and *Vibrio harveyi*	Biofilm creation	(20 – 80 µg ml^{-1})	*Ns*EO-AuNPs efficiently restricted the biofilm creation of *S. aureus* and *V. harveyi* by reducing the hydrophobicity index (78% and 46% correspondingly)	[171]
Au nanoparticles loaded with gentamicin (GPA NPs) (180nm)	*P. aeruginosa or S. aureus, E. coli,* and *L. monocytogenes*	Biofilm creation	(0.116mg/mL)	The produced GPA NPs sustained their antibiotic functions against planktonic bacteria, but more effective to impair established biofilms and limited biofilm creation of pathogens including Gram-positive and Gram-negative bacteria.	[187]
Chitosan–streptomycin gold nanoparticles (CA NPs) (31 nm - 45 nm)	*P. aeruginosa*, *Salmonella typhimurium*, *L. monocytogenes*, and *S. aureus*	Biofilm creation	(125, 250, 500 µg/mL)	These findings highlighted that CA NPs were capable of dispersing the available biofilms constructed by Gram-negative and positive organisms like as *P. aeruginosa*, *Salmonella typhimurium*, *L. monocytogenes*, and *S. Aureus*	[188]
N-acylated homoserine lactonase proteins (AiiAAuNPs) (10 to 30 nm)	Multidrug-resistant *Proteus* species (*Proteus* strains DPr1, DPr2, and DPr3 and *P. vulgaris* ATCC 49565)	Biofilm creation	(2 to 8 µM)	AiiAAuNPs restricted the *in vitro* biofilm creation in addition to the virulence factor (exopolysaccharide) generation and metabolic function of *Proteus*.	[189]
Au–Ag NPs (~20 nm)	*E. coli*, *P. aeruginosa*, *Enterococcus faecalis* and *S. aureus*.	Biofilm creation	(10, 150, 100, 250, and 150 µM)	Au–Ag NPs were additionally observed to be an efficient biofilm restricting agent	[190]
BisBAL NPs (28 nm)	*Streptococcus mutans, L. casei. Streptococcus gordonii*and *C. albicans*	Biofilm creation	100 µM	The findings illustrated a near-complete restriction of biofilm creation. Therefore, BisBAL NPs is viewed as antimicrobial agents to manage biofilm creation through a complicated combination of microbes.	[191]
BisBAL NPs (18 nm)	*P. aeruginosa*	Biofilm creation	12·5 µM	Lipophilic BisBAL nanoparticles restricted bacterial adherence to track-etched polycarbonate membrane surfaces and lysed bacteria implanted in biofilms, within 1 h of exposure. Therefore, lipophilic bismuth nanoparticles are potential antimicrobial agents that have the ability to restrict development, avoid bacterial adherence to surfaces or impair available biofilms.	[192]
Bi-NPs (3.3 ± 0.97 nm)	*S. mutans*	Biofilm creation	0.5 mM	Zerovalent bismuth nanoparticles entirely avoided biofilm creation. Zerovalent bismuth nanoparticles would only decrease cell development and not entirely restrict it. It is theorised that, as 69% of cells were inactivated by these nanoparticles, cell survival was not adequate to create a biofilm.	[193]

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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