



Nanoparticles as therapeutic options for treating multidrug-resistant bacteria: research progress, challenges, and prospects

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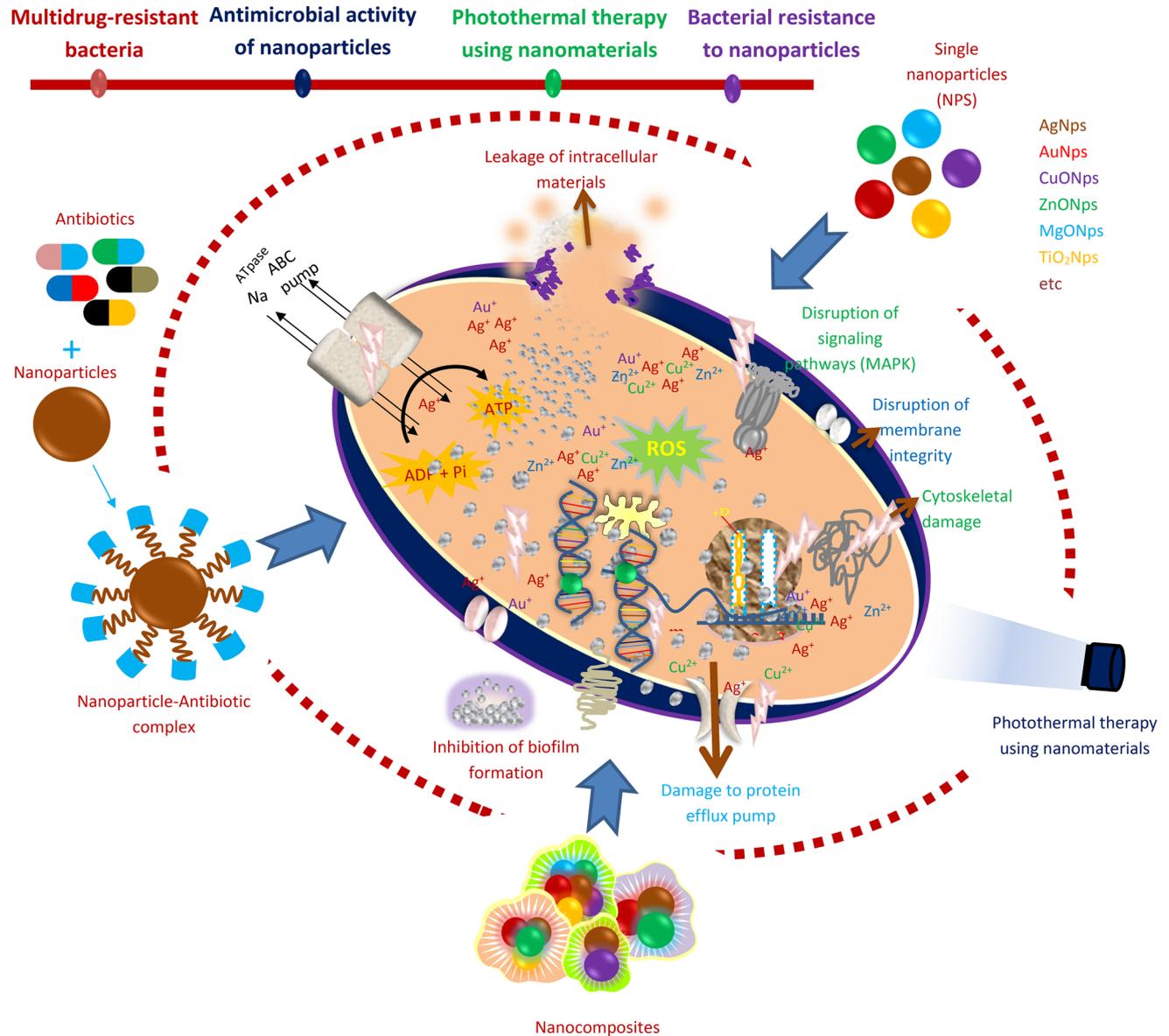
Abstract

Resistance to antimicrobial agents has been alarming in recent years and poses a huge public health threat globally according to the WHO. The increase in morbidity and mortality resulting from microbial infections has been attributed to the emergence of multidrug-resistant microbes. Associated with the increase in multidrug resistance is the lack of new and effective antimicrobials. This has led to global initiatives to identify novel and more effective antimicrobial agents in addition to discovering novel and effective drug delivery and targeting methods. The use of nanoparticles as novel biomaterials to fully achieve this feat is currently gaining global attention. Nanoparticles could become an indispensable viable therapeutic option for treating drug-resistant infections. Of all the nanoparticles, the metals and metal oxide nanoparticles appear to offer the most promise and have attracted tremendous interest from many researchers. Moreover, the use of nanomaterials in photothermal therapy has received considerable attention over the years. This review provides current insight on antimicrobial resistance as well as the mechanisms of nanoparticle antibacterial activity. It offers an in-depth review of all the recent findings in the use of nanomaterials as agents against multi-resistant pathogenic bacteria. Also, nanomaterials that can respond to light stimuli (photothermal therapy) to kill microbes and facilitate enhanced drug delivery and release are discussed. Moreover, the synergistic interactions of nanoparticles with antibiotics and other nanomaterials, microbial adaptation strategies to nanoparticles, current challenges, and future prospects were extensively discussed.

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Graphic abstract



Keywords Nanoparticles · Antimicrobial resistance · Conjugated nanoparticles/nanocomposites · Photothermal therapy · Antibacterial activity · Bacterial resistance to nanoparticles

Introduction

Nanoparticles are biomaterials with dimensions between 1 and 100 nm (nm). Considerable attention has been given to nanomaterials due to their wide application in agriculture, pharmaceuticals, consumer products, transportation, energy, cosmetics, and more importantly as antimicrobial agents. They are currently regarded as viable substitutes and/or supplements to existing antimicrobials (Li et al. 2017).

Generally, nanoparticles' antimicrobial or biomedical properties depend on their methods of synthesis and formulation conditions, such as the nature of the reducing agent, temperature, concentration, and solvent type (Lee et al. 2019; Qing et al. 2018; Kedziora et al. 2018). The actions and activity of these nanoparticles also mostly depend on their chemical composition, shape and size (Shobha et al. 2014). Several conditions and parameters need to be modified and varied to produce a nanoparticle with effective size, distribution,

morphologies, and yield. Factors like temperature, pH and metal ion concentration, cell age, and time of reaction also affect the antimicrobial activity of nanoparticles. For an increase in their activity, nanoparticles can be coated with several coating agents (Jaworski et al. 2018). Surface stabilizers, surfactants, polymers and oligonucleotides can be used as coating agents. These capping agents help to stabilize the nanoparticles against agglomeration.

Nanoparticles can either be organic (e.g., liposomes, polymeric, micelles, ferritin) or inorganic (e.g., metal nanoparticles). Both types of nanoparticles have been influential in treating several health conditions (Anselmo and Mitragotri 2016). Organic nanoparticles have been used to increase the bioavailability of drugs, enhance efficient drug delivery and improve antibacterial activity (Yetisgin et al. 2020). They have also been used in treating fungal infection (Mba and Nweze 2020) and have shown promises against viral infections [e.g., severe acute respiratory syndrome 2 (SARS-CoV-2)] infection (Mba et al. 2021). Currently, available nanoparticulate antibacterial systems include liposomes, polymeric NPs, micelles, solid lipid NPs (SLNs), nanostructured lipid carriers (NLCs), nanocapsules, nanotubes, quantum dots, dendrimers, emulsions, nanogels, and vesicles. They are nano-scale drug delivery systems that offer a slow-release and the delivery of drugs to the targeted cells.

The metallic nanoparticles appear to be the most promising. They exhibit diverse activities against several multidrug resistant pathogens (Liao et al. 2019; Rasheed et al. 2017; Mba and Nweze 2020). The most widely studied metal nanoparticles are silver nanoparticles (AgNps) and gold nanoparticles (AuNps). Metallic oxide nanoparticles with proven antibacterial activities include copper oxide nanoparticles (CuONps), zinc oxide nanoparticles (ZnONps), titanium oxide nanoparticles (TiO₂Nps), and magnesium oxide nanoparticles (MgONps). Others include calcium oxide nanoparticles (CaONps), iron oxide nanoparticles (Fe₂O₃Nps) and manganese oxide (MnO₂Nps). AgNps is the most studied and most widely used among all the nanoparticles (Mohler et al. 2018). Nanoparticles can also be combined with antibiotics and other nanomaterials for improved antibacterial activity.

Moreover, the light-responsive technique specifically has been used in the development of drugs. It has also found application in the design of drug carrier systems. The light-responsive structure can easily be regulated, and it has low invasiveness (Thang et al. 2019). Its mechanism of activity is based on the alteration of the light-sensitive molecules when stimulated by light, thus enabling the release of the encapsulated or conjugated drug (Linsley and Wu 2017). Over the years, the use of nanomaterials in photothermal therapy has received considerable attention. Several organic and polymeric nanoparticles have been reported to exhibit inherent photothermal ability (Zhao et al. 2018).

Therefore, in the face of increasing resistance to frontline antimicrobial agents and the rise in infections mostly caused by multidrug-resistant organisms, researchers have made efforts to develop alternative therapeutic approaches. The application of nanotechnology appears to be a viable solution due to the distinctive properties of nanomaterials. This review provides an important update on the issue of antimicrobial resistance. Based on recent literature, the mechanism of antimicrobial activity displayed by nanoparticles are discussed. Recent investigations reporting the activity of nanoparticles against drug-resistant bacteria are also highlighted. Moreover, insight on the synergistic activity of nanoparticles with antibiotics and other nanomaterials are also discussed extensively. Also, nanomaterials that can respond to light stimuli (photothermal therapy) to kill microbes and facilitate enhanced drug delivery and release are discussed. Finally, the recently emerging adaptive response tactics of bacteria to nanoparticles and current challenges in the use of nanoparticles as well as their future prospects are also presented.

The burden of antibiotic resistance and the need for antibacterial nanomaterials

The response of microbes to antimicrobial attack is an important illustration of adaptation and the pinnacle of evolution. Studies have shown that microbial infection is responsible for about 3 million deaths in developing countries annually. It also causes about 10 million deaths annually, mostly in the tropical countries (Dye 2014; Global Health Estimate 2016; Fenollar and Mediannikov 2018) despite the vast advances in diagnoses and therapeutics that have been achieved over the years. Developed countries are not spared either. Antimicrobial drug resistance has become a major global public health issue in medicine. In the US alone, the estimated economic burden associated with multidrug-resistant (MDR) microbes is about \$20 billion dollars yearly (Munita and Arias 2016). The issue of resistance often leaves clinicians with no reliable alternative to manage infected patients. Also, the emergence of multidrug resistant bacteria and super bacteria (bacteria resistant to almost all antibiotics) has compounded the problem. This is broadly associated with the excessive use of antibiotics which subsequently facilitates the generation and evolution of strains with genotypic and phenotypic diversities (Wang et al. 2017a, b).

Therefore, emergence of MDR and extensively-drug resistant (XDR) bacteria persist as a critical challenge in public health as it is associated with high mortality, morbidity, and high cost of treatment (Sanchez et al. 2013; Roca et al. 2015). This is further exacerbated by the ability of several bacterial strains to form biofilms, which is associated with about 65–80% of human infections (Lebeaux et al.

2013). Cells in biofilms are usually 100–1000 times less susceptible to antibiotics than planktonic cells (Saginur et al. 2006). The increase in resistance of drugs by biofilms is due to several factors: decrease in drug penetration across the extracellular matrix, reduction in drug concentration, reduction in metabolic rates of bacteria, and transfer of resistant genes (Hall-Stoodley et al. 2004; Hall and Mah 2017). MDR *S. aureus* and *P. aeruginosa* are the leading causes of chronic biofilm-associated infections worldwide, often characterized by a slower rate of wound healing, failure of catheters, and prolonged hospital stays (Nathwani et al. 2014; Sanchez et al. 2013).

Furthermore, antimicrobial drug resistance is among the three most important global public health threats identified in the twenty-first century by the World Health Organization (WHO). The ESKAPE group (*Enterococcus*, *Staphylococcus*, *Klebsiella*, *Actinobacter*, *Pseudomonas*, *Enterobacter*) are the most critical and have raised the most concerns. They are all associated with a high mortality rate. Based on reports from WHO, about 80% of the MDR or XDR microbes are due to misuse and overuse of antibiotics, and these infections are associated with severe adverse effects. Currently, there are limited therapeutic and prevention options due to the expansion of MDR bacteria and other resistant pathogens. There is a need for alternative therapeutic options for microbial pathogens. The failure of most antibiotics necessitates the search for better treatment options. Also, for effective infection control, drugs that can treat infection with the smallest possible dose is an appropriate approach (Morgan et al. 2011; WHO 2015).

Nanotechnology is a promising therapeutic strategy due to its high efficacy and therapeutic index against microbes (Hussain et al. 2018). Nanoparticles offer a viable alternative in the management of most bacterial infections, especially those involving multi-drug resistant organisms. Nanoparticles can be used singly or combined with antibiotics providing excellent synergistic effects. Nanomaterials that can respond to diverse endogenous and exogenous stimuli to killed microbes and also facilitate enhanced drug deliver and release are promising strategies (Hsiao et al. 2015; Qiu et al. 2018).

Metallic and metal oxide nanoparticles are promising antibacterial agents

AgNps are currently seen as the next generation antibiotics. This is because of their high effectiveness in inhibiting microorganisms. Currently, AgNps are the leading nanoparticles among all the commercialized nanomaterials (Arya et al. 2019). Research into their use as antimicrobial agents has intensified over the years due to their reduced toxicity when compared to other nanoparticles. Attachment and

penetration of the AgNps nanoparticles to microbial membrane surface is usually the first step in its cytotoxic mechanism (Singh et al. 2015). The damage to internal components is caused by the released Ag⁺ ions which trigger the generation of ROS and subsequent oxidative stress induction which affect the Na⁺/K⁺ ATPase pump and signal transduction pathways (Singh et al. 2015; Flores-Lopez et al. 2019). Ag⁺ ions and AgNps also interact with DNA (phosphorus-containing compounds) leading to protein inactivation and subsequent cell death. In fact, sulphur, chlorine, thiols, and oxygen can interact with a great effect on Ag⁺ ion release (Maurer and Meyer 2016).

Also, the rate at which this Ag⁺ ion is released is largely affected by the size (Sriram et al. 2012; Abuayyash et al. 2018). Small size AgNps can easily penetrate the cell wall. They also alter the structural integrity and membrane architecture causing an increase in permeability and subsequent cell apoptosis. The type of bacterial species also influences AgNps activity. This is because of the different cell wall composition, thickness, and arrangement (Tamayo et al. 2014). The precise antimicrobial activity of AgNps beside the generation of ROS is associated with the cell wall and plasma membrane damage according to Hamouda et al. (2019). This is because of protein inactivation and membrane lipid peroxidation. These activities modify the structural membrane integrity leading to the disorder of the transport proteins. It also causes potassium leakage.

AuNps are among the most widely researched nanoparticles with good antimicrobial activity (Shamaila et al. 2016; Tao 2018; Bilal et al. 2017). AuNps exhibit several shapes including triangular, spherical, hexagonal, and even rod-like shapes (Abdel-Raouf et al. 2017). The triangular-shaped AuNps as previously reported by Smitha and Gopchandran (2013) exhibit strong antibacterial activity against several bacteria compared to spherically-shaped AuNps. AuNps adhere to the membrane via electrostatic interaction and disrupt membrane integrity (Kundu 2017). They can cause leakage of intracellular components by generating holes in the membrane. AuNps can bind to DNA inhibiting replication and transcription. They can also aggregate with biofilm formed by microbes. Interactions between AuNps also provoked the formation of ROS essential for cell death. They alter membrane potential and decrease ATP synthase activities thereby reducing several metabolic activities. AuNps just like AgNps disrupt cell membrane integrity and structure (Rattanata et al. 2016). AuNps prevent rRNA from binding to its subunits, thus preventing translation (Cui et al. 2012). AuNps also interact with sulphur or phosphorus-containing nucleotides. AuNps supplemented with antibiotics usually shows strong antibacterial activity. According to a study by Brown et al. (2012), ampicillin integrated with AuNp was strongly effective against bacteria (*P. aeruginosa*, *E. coli*, *Enterobacter aerogenes* and MRSA) resistant to

ampicillin. The AuNp-AMP complex disrupts and inhibits the transmembrane pump catalyzing drug efflux. The AuNp-AMP also overwhelmingly neutralizes the high β -lactamase expressed by the bacteria.

Furthermore, copper/copper oxide nanoparticles (CuNps/CuONps) exhibit antimicrobial activity (El-Batal et al. 2017; Asemani and Anarjan 2019). Available report suggests that its antimicrobial activity is derived via the electrostatic attraction between the nanoparticle and the cell (Bogdanovic et al. 2014). The Cu^{2+} ion can also bypass the lipid bilayer and gain access into the cell. Upon penetration into the cell, it triggers the production of ROS. Lipid peroxidation and protein oxidation is also evident (DeAlba-Montero et al. 2017). The ability of Cu to alternate between +1 and +2 oxidation state is also responsible for its antimicrobial activity. A recent investigation reported that CuONps can interact with amino acids with a great influence on its bacterial activity (Badetti et al. 2019).

ZnO nanoparticle is also a promising antibacterial agent (Bhuyan et al. 2015). It was previously reported that surface coating of ZnONps could prevent their interactions with biological fluid. However, Pranjali et al. (2019) found that PEGylated ZnONps strongly bind and interact with peritoneal dialysis (PD) fluid, lactic and citric acids leading to agglomeration. In addition, a drastic decrease in the bacterial inhibition effect was observed for both the ZnONps and the PEG-coated ZnONps dispersed in biological fluid. ZnONps release Zn^{2+} ions when in contact with the microbial cell. The Zn^{2+} ions disrupt the cell membrane. The interaction between the ions and several intracellular components further causes more harm to the cell (Li et al. 2011). In addition, Zn^{2+} causes the generation of ROS (Kumar et al. 2011; Singh et al. 2020). Recently, Nejabatdoust et al. (2019) reported that ZnONps conjugated with thiosemicarbazide and functionalized by glutamic acid modifies the expression of efflux pump genes in multiple drug-resistant *S. aureus*.

TiO_2 Np produces ROS which is responsible for cell membrane damage and disruption of oxidative phosphorylation (Singh et al. 2018). TiO_2 Np also inactivates signaling pathways, reduces the co-enzyme-independent respiratory network as well as the take-up and transport of Fe and P. It also decreases the biosynthesis and degradation of heme group (Foster et al. 2011). Its activity is also photo dependent. The generation of free radicals has also been reported (Wu et al. 2010). Evidence is also available that it can damage the peptidoglycan, lipopolysaccharide, in addition to the phospholipid bilayer (Liu et al. 2010). Similarly, MgONp can produce ROS that is highly detrimental to cells (Krishnamoorthy et al. 2012; He et al. 2016). Nguyen et al. (2018) reported that MgONps reduce biofilm forming ability of *S. epidermidis* and damages the membrane of *E. coli* causing cell apoptosis. The authors suggested that the production of ROS, Ca^{2+} concentrations and quorum sensing are the

mechanisms contributing to their antimicrobial activity. In addition, the MgONp cell surface attachment damages membrane integrity and cause leakage of intracellular components. In a recent study, MgONps and MnONps were biosynthesized using *Matricaria chamomilla* L extract. The results showed that the nanoparticles invade the cells and damage the membrane. This led to the leakage of intracellular cytoplasmic content (Ogungemi et al. 2019). According to Ogungemi et al. (2019) MgONp antimicrobial activity is also achieved by the production of Mg^{2+} ion, cell membrane interaction and pH changes.

Also, a recent study showed that Fe_3O_4 Nps reduce H^+ -flux through bacterial membrane. Fe_3O_4 Nps specifically inhibit ATP-associated metabolism. There was also a decrease in membranes associated H_2 production (Gabrielyan et al. 2019). Several researchers have investigated the antimicrobial activity of biosynthesized FeNps and Fe_2O_3 Nps (Sathishkumar et al. 2018; Jagathesan and Rajiv 2018; Madivoli et al. 2019). Studies are also available reporting the antimicrobial potentials of calcium oxide nanoparticles (Butt et al. 2015; Balaganesh et al. 2018; Pasupathy and Rajamanickam 2019; Gurav et al. 2020). Figure 1 summarizes the mechanisms of antibacterial activity of nanoparticles while Table 1 shows the recent studies reporting the antimicrobial activity of nanoparticles.

Synergistic antimicrobial activity of nanoparticles

The activities of nanoparticles can be greatly enhanced when conjugated or coated with other materials. In fact, combining nanoparticles with antibiotics can help reduce microbial resistance. In resistant strains, variation in the mode of action of antibiotics and the nanoparticles enhance the susceptibility of the microbe. If a particular strain is resistant to one antimicrobial agent, another antimicrobial agent could trigger the killing by using a different mechanism. The nanoparticles can also act as carriers of antibiotics thereby facilitating access to bacterial cell walls. The antibiotic in turn damages the cell wall enabling easy entry of the nanoparticles and its complex.

In a study that combined amoxicillin with AgNps, a significant reduction in growth of bacteria was evident (Li et al. 2005). The transport of amoxicillin across the microbial membrane was facilitated by the hydrophobic nature of the AgNps which interact with the cell membrane. Duran et al. (2010) showed that AgNps and amoxicillin synergistic activity was due to sulfur bridge formation between the two agents. Fayaz et al. (2010) showed that AgNps-ampicillin complex inhibits the formation of crosslinks in the peptidoglycan layer leading to cell death. This complex also prevented the unwinding of DNA. It was reported

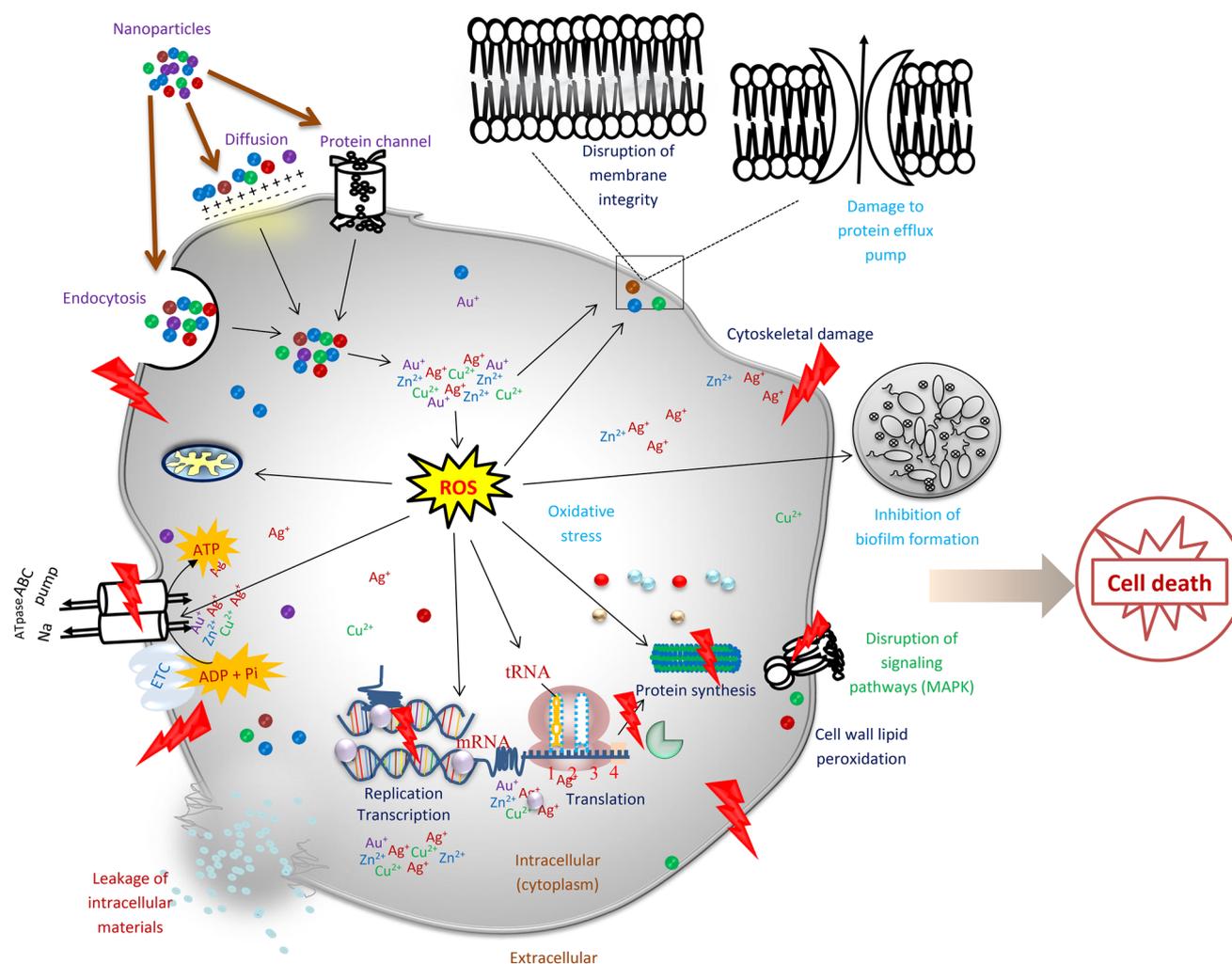


Fig. 1 Mechanism of nanoparticles activity against bacteria

by Panacek et al. (2015) that a very low concentration of AgNps is needed for synergistic activity with antibiotics with no cytotoxic effect. Wan et al. (2016) showed the synergistic activity of AgNps combined with polymyxin B and rifampicin against *A. baumannii*. It was also reported by Banoee et al. (2010) that ZnONps-ciprofloxacin complex interrupts with the endogenous efflux transporter (NorA) and the Omf proteins which facilitate the entrance of ciprofloxacin into the cell. The synergistic activity of TiO₂Nps and several antibiotics against MRSA was also studied by Roy et al. (2010). Significant antibacterial activity was observed. However, the exact mechanism of its synergistic activity is yet to be elucidated. Chamundeeswari et al. (2010) reported that AgNps-ampicillin complex exhibit greater antimicrobial activity against *S. aureus*, *E. coli* and *K. mobilis* than single amoxicillin.

In a more recent investigation, Farzana et al. (2017) reported the antimicrobial behavior of ZnONps and β -lactam

antibiotics against bacteria. AuNps-antibiotics complex also exhibited excellent antimicrobial activity (Shaikh et al. 2019). Mohamed (2020) reported that AuNps conjugated with ampicillin/amoxicillin showed significant antibacterial activity and was biocompatible with treated cells. Farooq et al. (2019) showed that rifampicin conjugated AgNps produced anti-biofilm activity against MRSA and *K. pneumonia*. Surwade et al. (2019) reported that AgNps combined with ampicillin showed very strong synergistic effects against MRSA. A similar result was provided by Sajjad et al. (2019) who studied the synergistic activity of AgO₂Nps and ceftriaxone against *E. coli*. Several other researchers have reported the synergistic effects of nanoparticles with antibiotics (Shahbazi et al. 2019; Gounani et al. 2018). Table 2 summarizes other studies that reported the synergistic activity of nanoparticles with antibiotics. Moreover, nanoparticles conjugated with specific antibody exhibit excellent activity against resistant pathogens. Al-Sharqi et al.

Table 1 Recent studies on nanoparticles showing the source, shape and size, organisms tested, antimicrobial potential and other key findings (cytotoxicity and reported mechanisms)

Nps	Source	Shape and size	Bacteria isolates tested	Antibacterial activity (IZD/MIC/MBC) and other key findings	Reference
AgNps	<i>Acacia rigidula</i> plant extract	Spherical Size distribution: 8–66 nm with mean of 22.46 nm Diameter size: 15–25 nm	<i>E. coli</i> , <i>P. aeruginosa</i> , Clinically MDR strain of <i>P. aeruginosa</i> and <i>B. subtilis</i>	In vitro: 62.5, 15.6, 7.8, and 0.5 ppm for <i>E. coli</i> , <i>P. aeruginosa</i> , multi-drug resistant <i>P. aeruginosa</i> and <i>B. subtilis</i> respectively In vivo: antimicrobial effect against the resistant pathogens tested in a murine skin infection model. Effective and safety use of Nps as therapeutic agents in animal models	Escarcega-Gonzalez et al. (2018)
AgNps	Biosynthesized using <i>Pseudoduganella eburnea</i> MAHUQ-39	Spherical 8–24 nm	Multidrug resistant pathogenic microbes <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>E. coli</i>	MIC of <i>S. aureus</i> and <i>P. aeruginosa</i> were 100 µg/ml respectively. MBC of <i>S. aureus</i> and <i>P. aeruginosa</i> were 200 and 50 µg/ml respectively Mechanism: structural alterations Disruption of the membrane integrity of strains <i>S. aureus</i> and <i>P. aeruginosa</i>	Huq (2020)
AgNps	Biosynthesized using <i>Sphingobium</i> sp-MAH-11	Spherical 7–22 nm	Drug resistant microbes <i>P. aeruginosa</i> , <i>E. coli</i> , <i>S. aureus</i>	MIC of <i>E. coli</i> and <i>S. aureus</i> were 6.25 and 50 µg/ml respectively and MBC of <i>E. coli</i> and <i>S. aureus</i> were 25 and 100 µg/ml respectively Mechanism: using <i>E. coli</i> and <i>S. aureus</i> , causes morphological alterations and disrupt membrane integrity of the isolates	Akter and Huq (2020)
AgNps	Green synthetic method and casein hydrolysate as a reducing reagent and NaOH as a catalyst	Spherical Average sizes: 10 ± 5 nm, 30 ± 5 nm, 60 ± 5 nm, 90 ± 5 nm	<i>Vibrio natriegens</i>	MIC and MBC were dose dependent. The smaller the particle the more bacterial damage. MIC ranges from 1 to 11.5 µg/ml and MBC, 1.1–11.7 µg/ml Mechanism: generation of ROS by bacteria and bacteria membrane damage	Dong et al. (2019)

Table 1 (continued)

Nps	Source	Shape and size	Bacteria isolates tested	Antibacterial activity (IZD/MIC/MBC) and other key findings	Reference
AgNps	Synthesized using aqueous and ethanolic extract of <i>Adrographis paniculata</i> stem	Spherical Ag-bAgNps- 24,90 nm Et-bAgNps-25.24 nm	Enteropathogenic <i>E. coli</i> , <i>S. typhi</i> , <i>S. aureus</i> , <i>V. cholerae</i> , <i>E. faecalis</i> , <i>Hafnia alvei</i> , <i>Acinetobacter baumannii</i> , <i>E. coli</i> DH5 α , <i>E. coli</i> K ₁₂ and <i>B. cereus</i>	Lowest MIC for both the bAgNps was 0.125 μ g. Et-bAgNps had the highest antibacterial activity against <i>S. aureus</i> at 60 μ g after 16 h and IZD was 28 mm Cytotoxicity: showed excellent hemocompatibility against human as well as rat RBC. No significant cytotoxicity observed when the levels of rat serum ALT, AST, γ -GT (liver function biomarkers) and creatinine (kidney function biomarker) were evaluated	Hossain et al. (2019)
AgNps	Synthesized using methanolic extract of <i>Oscillatoria</i> spp.	Spherical 10 nm	<i>S. aureus</i> , <i>E. coli</i> 11,775, <i>E. coli</i> 35,218, <i>P. aeruginosa</i> , <i>Citrobacter</i> Spp., <i>Salmonella typhi</i> 14,028, <i>B. cereus</i>	Effective antibacterial activity against all pathogens with IZD ranging from 1 to 21 mm Antibiofilm: exhibit strong antibi-offil activity Cytotoxicity: Using <i>Artemia salina</i> (brine shrimp), it was observed to be insignificant with the highest mortality at 4000 μ g/ml and LC50 of 2630.3 μ g/ml	Adebayo-Tayo et al.(2019)
AgNps	Synthesized using mycelial extract of endophytic fungus <i>Talaromyces purpureogenus</i>	Triangular shaped 25 nm	<i>S. aureus</i> , <i>B. cereus</i> , <i>S. enterica</i> , <i>P. aeruginosa</i> , <i>E. coli</i>	MIC of 16.12 μ g/ml for gram positive and 13.98 μ g/ml for gram negative Cytotoxicity: Not toxic to normal NIH3T3 cells. Showed cytotoxicity in A549 cells even at the lowest concentration of 2 μ g/ml. Cytotoxicity increases with the increase of Nps concentration. IC50 for AgNps and AgNO3 was 376.24 and 250.31 μ g/ml respectively. 5.92% of cell apoptosis was induced by the Nps	Hu et al. (2019)
AgNps	<i>Fusarium scirpi</i> (fungi)	Quasi-spherical 2-20 nm	Uropathogenic <i>E. coli</i>	MIC of 25 mg/ml. Sub-MIC concentration (7.5 mg/l) was enough to inhibit the pathogen biofilm formation about 97% or produce the disruption of 80% of mature biofilm	Rodriguez-Serrano et al. (2020)

Table 1 (continued)

Nps	Source	Shape and size	Bacteria isolates tested	Antibacterial activity (IZD/MIC/MBC) and other key findings	Reference
AgNps	Aqueous extract of <i>Cyanobacterium oscillatoria</i>	Spherical 3.30–17.97 nm	<i>E. coli</i> , <i>B. cereus</i>	IZD of 22 mm and 20 mm Mechanism: damage to cell membrane, leakage of cytoplasm exterior to cell, Internal diffusing of AgNps to cell, cell disruption, disintegration, Shrinking of protoplasm and, detachment of cellular membrane Cytotoxicity: hemolytic activity showed that it was non-toxic to human RBC in low concentrations	Hamouda et al., (2019)
AgNps	Aqueous extract of black pomegranate peels	Spherical 32–85 nm	<i>P. aeruginosa</i>	Showed strong inhibition against biofilm formation at 0.1–0.5 mg/ml Cytotoxicity: no significant toxicity against L929 cell line at 400 µg/ml	Habibipour et al., (2019)
AgNps	Synthesized by <i>Fusarium solani</i>	Spherical 13.70 nm	Multidrug resistant <i>P. aeruginosa</i> and <i>S. aureus</i>	Showed significant effect against <i>P. aeruginosa</i> (22.4 mm) and MIC of 21.33 µg/ml Mechanism: formation of cracks and pits in the cell wall when nanoparticles were internalized	El-Sayed and El-Sayed (2020)
AgNps	Biosynthesized using <i>Xianghaensis</i> OF1 strain	Spherical 64 nm	<i>P. aeruginosa</i> , <i>M. furfur</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>S. aureus</i> and <i>K. pneumonia</i>	MIC of 16, 32, 64, 64, 256, 26 µg/ml respectively Cytotoxicity: in vitro cytotoxicity against mouse fibroblasts and cancer HeLa cell lines showed dose dependent activity, IC50 was found in concentration of 4 and 3.8 µg/ml	Wypig et al. (2018)
AuNps	Aqueous extract of <i>Euprasia officinalis</i>	Quasi-spherical 49.72 ± 1.2 nm	<i>P. aeruginosa</i> , <i>E. coli</i> , <i>S. aureus</i> and <i>Vibrio parahaemolyticus</i>	Antibacterial activity: 15.3 ± 0.5 ppm, 11.7 ± 0.5 ppm, 14.7 ± 0.9 ppm and 13.7 ± 1.1 ppm Cytotoxicity: inhibit human cervical cancer cells (HeLa) at 10 µg/ml but did not inhibit human lung cancer cells (A549)	Singh et al. (2018)
AuNps	Leaf extract of <i>Annona muricata</i>	Spherical 25.5 nm	<i>S. aureus</i> , <i>Clostridium sporogenes</i> , <i>E. faecalis</i> and <i>K. pneumonia</i>	Exhibit good antimicrobial activity with increase in concentration	Folorunso et al. (2019)

Table 1 (continued)

Nps	Source	Shape and size	Bacteria isolates tested	Antibacterial activity (IZD/MIC/MBC) and other key findings	Reference
ZnONps	<i>Albizia lebbek</i> stem bark	Spherical 66.25 nm	<i>B. cereus</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , and <i>S. typhi</i>	Exhibit strong antimicrobial activity which was dose dependent Cytotoxicity: MDA-MB231 and MCF-7 cell lines Cytotoxic effect was concentration dependent	Umar et al. (2019)
ZnONps	<i>Bacillus haynesii</i>	Spherical 50±5 nm	<i>E. coli</i> ATCC 35,218, <i>S. aureus</i> ATCC 29,213	MIC and MBC values were > 8 and 16 mg/ml respectively for <i>E. coli</i> and 4 and 8 mg/ml respectively for <i>S. aureus</i>	Rehman et al. (2019)
ZnONps	<i>Cinnamomum verum</i> bark extract	Hexagonal wurtzite 45 nm	<i>E. coli</i> MTCC 7443 and <i>S. aureus</i> MTCC 7410	MIC of 125 µg/ml for <i>E. coli</i> and MIC OF 62.5 µg/ml for <i>S. aureus</i>	Ansari et al. (2020)
ZnONps	<i>Boswellia ovalifoliolata</i>	Spherical 20.3 nm	<i>Sphingobacterium</i> sp., <i>Acinetobacter</i> sp., <i>Ochrobactrum</i> sp.	IZD: 3 mm, 1.7 mm and 4 mm	Supraja et al. (2016)
ZnONps	<i>Withania somnifera</i> (ws) leaf extract	Hexagonal wurtzite 15.6 nm	<i>E. faecalis</i> , <i>S. aureus</i> , <i>E. coli</i> and <i>P. aeruginosa</i>	A greater antibacterial effect of ws-ZnONps was noticed against <i>E. faecalis</i> and <i>S. aureus</i> at 100µg/ml. The biofilm of <i>E. faecalis</i> and <i>S. aureus</i> were greatly inhibited at 100µg/ml compared to <i>E. coli</i> and <i>P. aeruginosa</i> . Cytotoxicity: larval and pupal development delayed at 25µg/ml. A complete mortality (100%) was observed at 25µg/ml. ws-ZnONps showed least LC50 value (9.65µg/ml) compared to the uncoated ZnONps (38.8µg/ml) and leaf extract (13.06µg/ml)	Malaikozhundan et al. (2020)
CuONps	Aqueous extract of <i>Abutilon indicum</i>	Hexagonal, wurtzite and sponge crystal structure 16.78	<i>Klebsiella</i> , <i>E. coli</i> , <i>S. aureus</i> , <i>B. subtilis</i>	Significant bactericidal activity of nanoparticle against <i>Klebsiella</i> and <i>B. subtilis</i> with IZD of 14 ± 005 and 15 ± 0.11 mm respectively. At 5 mg, the CuONps showed effective activity against <i>S. aureus</i> , <i>Klebsiella</i> , <i>B. subtilis</i> with IZD of 10 ± 0.11, 14 ± 0.05 and 15 ± 0.11 mm respectively	Ijaz et al. (2017)

Table 1 (continued)

Nps	Source	Shape and size	Bacteria isolates tested	Antibacterial activity (IZD/MIC/MBC) and other key findings	Reference
CuONps	Aqueous extract of <i>Tamarindus indica</i> fruit	Cube shaped 40–50 nm	<i>Proteus mirabilis</i> , <i>S. aureus</i>	Significant synergistic effect with β -lactam antibiotics Reduction in biofilm formation of the two organisms by 85% and 93% respectively	Selvaraj et al. (2019)
CuONps	Leaf extract of <i>Aloe barbadensis</i>	Spherical 33.4–64.9 nm	<i>Pseudomonas</i> , <i>Klebsiella</i> , <i>Staphylococcus</i> , <i>E. coli</i>	IZD of 11, 12, 8 and 9 mm respectively	Saruchi et al. (2019)
TiO ₂ Nps	Synthesized using <i>S. aureus</i>	Spherical 20 nm–30 nm	<i>E. coli</i> , <i>B. cereus</i> , <i>S. aureus</i>	Highly effective against <i>B. subtilis</i> (9 mm) and <i>E. coli</i> (14 mm) Showed antibiofilm activity against the pathogens	Landage et al. (2020)
TiO ₂ Nps	Laser ablation	Round (circular) 36 nm	<i>S. aureus</i> , <i>E. coli</i>	In distilled water, the MIC is 9.45 mg/ml and 18.91 mg/ml for <i>E. coli</i> and <i>S. aureus</i> respectively. In alcohol, the MIC is 4.72 mg/l for <i>E. coli</i> and 9.45 mg/l for <i>S. aureus</i>	Abdul-Hussan et al. (2018)
MgONps	Aqueous extract of <i>Sweria chirayita</i>	Spherical <20 nm	<i>S. aureus</i> MTCC9442, <i>S. epidermidis</i> MTCC 2639, <i>B. cereus</i> MTCC-9017, <i>E. coli</i> MTCC 9721, <i>Proteus vulgaris</i> MTCC7299, <i>K. pneumonia</i> MTCC9751	Antimicrobial activity was dose dependent The IZD of the various MgONps concentrations (10, 20, 30 and 40 μ l)(0.25 μ g/ml) were 18 mm for <i>E. coli</i> and 17 mm for <i>S. aureus</i> , which were also the maximum IZD for all the tested bacteria respectively. Moreover, a 16 mm IZD was obtained for <i>B. cereus</i> , <i>K. pneumonia</i> and <i>P. vulgaris</i>	Sharma et al. (2017)
MgONps	Leaf extracts of <i>Rhododendron arboretum</i>	Sphere shaped –	<i>E. coli</i> , <i>Streptococcus mutans</i> , <i>Proteus vulgaris</i>	Inhibition was dose-dependent and increased with increase in concentration. At 10 mg/ml of MgONps, IZD were 36 mm, 32 mm, 24 mm for <i>E. coli</i> , <i>S. mutans</i> and <i>Proteus vulgaris</i> respectively	Singh et al. (2019)
MgONps	<i>Trigonella foenum-graecum</i> leaf extract	Spherical 13 nm	<i>E. coli</i> , <i>Bacillus</i> , <i>S. aureus</i>	Good antibacterial activity: 125 μ g, 250 μ g, 125 μ g	Vergheese ans Vishal (2018)

Table 1 (continued)

Nps	Source	Shape and size	Bacteria isolates tested	Antibacterial activity (IZD/MIC/MBC) and other key findings	Reference
MgONps	Commercial	Polyhedral morphology 20 nm	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. aureus</i> , <i>S. epidermidis</i> , MRSA	The MIC varied from 0.5 to 1.2 mg/ml. The minimal lethal concentration (MLC) at 90% killing varied from 0.7 to 1.4 mg/ml against the various pathogens. The most potent concentration (MPC) was 1.4 and or 1.6 mg/ml—this depends on the organism tested Mechanism: reduction in adhesion, disruption of biofilm formation, production of ROS, quorum sensing and Ca ²⁺ concentrations	Nguyen et al. (2018)

(2019) reported that AgNps conjugated with specific antibody showed good antimicrobial activity against *S. aureus*.

While nanoparticle-antibiotic complex provides a strong synergism against pathogenic microbes, the combination of two different nanoparticles can help improve their activity while reducing their toxicity. Coating nanoparticles with biomaterials can also enhance their activity. Coating AgNps with TiO₂ or other metal or metallic oxide materials enhances its antimicrobial activity. Hu et al. (2017) showed that ZnO/Ag bimetallic nanoflowers exhibit improved antibacterial activity. Recent studies by Jaworski et al. (2018) and Cobos et al. (2020) showed that AgNps decorated with graphene oxide nanocomposites exhibit strong antibacterial activity. Nunez et al. (2019) also showed that nanohybrids mediated AgNps was effective against Gram positive and Gram-negative microbes (Nunez et al. 2019). Table 3 summarizes some recent studies on nanocomposites/nanohybrids.

Photothermal therapy using nanomaterials is a promising approach to combat antimicrobial resistance

Over the years, the use of nanomaterials in photo thermal therapy has received considerable attention (Wei et al. 2018; Canaparo et al. 2019; Ramezani et al. 2020). The light-responsive technique specifically has been used in the development of drugs. It has also found application in the design of drug carrier systems and as an antibacterial agent (Qi et al. 2019). The light-responsive structure can be easily regulated and it has low invasiveness (Bao et al. 2016). Its mechanism of activity is based on the alteration of the light-sensitive molecules when stimulated by light, thus enabling the release of the encapsulated or conjugated drug (Chen and Zhao 2018).

For the treatment of cancer, photothermal therapy uses the thermal stress caused by irradiation of light of a specific wavelength (Cheng et al. 2014a). They have also been used for the delivery of anticancer drugs (Yu et al. 2020). Although photothermal therapy has found application in the treatment of cancer, it is effective at killing pathogens irrespective of their drug resistance level or their metabolic state within the biofilm (Galanzha et al. 2012). Halstead et al. (2016) showed that blue light has a broad-spectrum antimicrobial activity against all six ESKAPE members. Further investigations also showed that low penetrating blue light of about 415 ± 10 nm is preferable for the treatment of wound infections as it is associated with low damage to the tissue cells (Wang et al. 2017a, b; Katayama et al. 2018). There was an inhibitory effect on bacterial growth in a study that exposed *P. aeruginosa* to light-emitting diode (LED) (Sueoka et al. 2018). The increase in antimicrobial activity was

Table 2 Nanoparticles combined with antibiotics for antimicrobial activity

Nanoparticles	Synthesis	Antibiotics	Organisms tested/Activity	Reference
AuNps	–	Ampicillin	2 strains of <i>S. aureus</i> MRSA Significant antibacterial activity, cytocompatible against human dermal fibroblasts	Fan et al. (2019)
CuNps	Green synthesis	Erythromycin Azithromycin Norfloxacin	<i>Klebsiella</i> , <i>Pseudomonas</i> , <i>E. coli</i> , <i>Shigella</i> <i>Staphylococcus</i> At 50, 100, 200, 400 µg/ml, all bacteria were resistant to antibiotics	Kaur et al. (2019)
AgNps	Synthesized using corn leaf waste of zea mays extract	Kenamycin Rifampicin	<i>Bacillus cereus</i> , <i>E. coli</i> , <i>S. aureus</i> , <i>L. monocytogenes</i> , <i>S. typhimurium</i>	Patra and Baek (2017)
AgNps	Synthesized using <i>Adiantum philippense</i> extract	Amoxicillin	MRSA	Kalita et al. (2016)
AgNps	Leaf extract of <i>Cassia roxburghii</i>	Ampicillin, Polymyxin, Clotrimazole Amikacin, Chloramphenicol, Penicillin-G, Tetracycline, Amoxiclav, Cefpirome Gentamycin, clotrimazole	<i>S. aureus</i> , <i>B. subtilis</i> , <i>E. coli</i> , <i>P. aeruginosa</i>	Moteriya et al. (2017)
AgNps	Spherical shaped Nps 8.57 ± 1.17 nm	Ampicillin, Amikacin	<i>E. faecium</i> , <i>S. aureus</i> , <i>A. baumannii</i> , <i>Enterobacter cloacae</i> , <i>E. coli</i> , <i>K. pneumonia</i> <i>Morganella morganii</i> , <i>P. aeruginosa</i> Excellent antimicrobial activity	Lopez-Carrizales et al. (2018)
CuNps	Synthesized using <i>Camellia sinensis</i> (green tea) and β-cyclodextrin	Penicillin, Streptomycin, Ampicillin Amoxicillin, Gentamicin, Ciprofloxacin	<i>S. pyrogenes</i> , <i>E. coli</i> , <i>S. typhi</i> , <i>Micrococcus lutus</i> <i>Streptococcus mutans</i>	Mandava et al. (2017)
Bimetallic Ag-Au nanoparticle	Synthesized using cell free supernatant of <i>P. veronii</i> strain AS41G on <i>Annona squamosa</i> L	Kanamycin, Bacitracin, Gentamycin Streptomycin, Erythromycin, Chloramphenicol	<i>E. coli</i> , <i>B. subtilis</i> , <i>K. pneumoniae</i>	Sharma et al. (2017)
ZnONps	–	Ciprofloxacin Ampicillin	<i>E. coli</i> (MTCC 739), <i>Klebsiella pneumonia</i> (MTCC 109), <i>P. aeruginosa</i> (MTCC 741), <i>Salmonella typhi</i> (MTCC 98), <i>S. aureus</i> (MTCC 737), <i>B. subtilis</i> (MTCC 736) Synergistic effects observed No antagonistic effect observed	Sharma and Jandaik (2016)
ZnONps	–	Ciprofloxacin Ceftazidime	<i>A. Baumannii</i> Combination caused increased uptake of antibiotic It changes the cells from rod to cocci form	Ghasemi and Halal (2016)

Table 2 (continued)

Nanoparticles	Synthesis	Antibiotics	Organisms tested/Activity	Reference
AgNps	–	B-lactam (ampicillin and penicillin) Quinolone (enoxacin) Aminoglycoside (kenamycin and neomycin) Polypeptide (tetracycline)	<i>Salmonella typhimurium</i> DT104 Kenamycin, Enoxacin, neomycin and tetracycline exhibited synergistic activity against the pathogen. Ampicillin and penicillin do not show any synergistic activity AgNps form complex with antibiotics (AgNps-tetracycline). The AgNps-tetracycline interact strongly with <i>Salmonella</i> causing Ag ⁺ release. The increase in Ag ⁺ concentration in the cell wall facilitate bacterial growth inhibition and subsequent death	Deng et al. (2016)

possible because the bacteria that withstand the initial PDT were subsequently affected by singlet oxygen produced due to the excitation of the remaining PS. Photothermal therapy leverage the plasmon resonance features of metals, especially AuNps. There is usually the absorption of energy in the visible light spectrum and the omission of energy as heat energy to the immediate medium (Jain et al. 2007; Mocan et al. 2014).

Several organic and polymeric nanoparticles have been reported to exhibit inherent photothermal ability (Zhao et al. 2018). Also, AuNps, iron oxide, black phosphorus, graphene, and many other polymeric nanoparticles with potential for photothermal conversion have been developed for antibiotic drug delivery (Ji et al. 2016; Hu et al. 2013) and chemo-photothermal therapy against pathogens under irradiation by NIR (Hu et al. 2013; Chiang et al. 2015; Meeker et al. 2016). Near-infrared (NIR) light is an excellent exogenous stimulus with promising potential against drug-resistant pathogens. The induction/activation of photothermal therapy (PTT) by NIR enables the PTT to enter deep into the tissue with little cytotoxicity. PTT can disrupt membrane permeability and signaling cascade of pathogenic organisms, disrupt key enzymes and proteins, and cause cell death (Ray et al. 2012; Kim et al. 2015; Korupalli et al. 2017). Kuang et al. (2017) demonstrated the photothermal therapeutic potential of IR-780 iodide (IR780) (a NIR fluorescence dye) encapsulated in cRGD-conjugated solid lipid nanoparticle. The low cytotoxicity, ease of been wrapped by hydrophobic carriers (inherent lipophilicity) and ease of degradation in the cell make IR780 a suitable agent for in vivo photothermal therapy (Ray et al. 2012). Also, under near-infrared (NIR) light irradiation, graphene-based nanomaterials exhibit high photothermal conversion

efficiency and outstanding, amphiphilicity. This attribute enables them to attach to the cell membrane of organisms enhancing nanoscale delivery of antimicrobial agents (Yuan et al. 2018; Ran et al. 2017).

Recently, it was shown that silica-coated gold-silver nanocages (Au–Ag@SiO₂ NCs) under NIR laser irradiation showed reliable increases in microbial resistance compared to Au–Ag NCs alone (Wu et al. 2019). Coating the Au–Ag NCs with silicon dioxide improved the surface plasmon resonance of Au–Ag NCs (Fig. 2). Also, upon irradiation of Au–Ag@SiO₂ NCs with NIR laser for 10 min, there was a swift temperature rise. Importantly, it was noticed that the increase in the concentration of Au–Ag@SiO₂ NCs and the time of laser irradiation correlated with a rise in temperature. This showed that the heat produced by this nanomaterial was rapid and able to eliminate *E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, and *Enterobacter* spp. (ESKAPE) pathogens.

Reports on bacterial resistance to nanoparticles are gradually emerging

Not minding the effectiveness of an antimicrobial agent, most microbes often find strategies to maneuver these agents. The flexibility of microbial genome and the selective pressure exerted by most biomaterials often facilitate the emergence of resistant. Thus, irrespective of the different mechanisms of nanoparticle activity against microbes, resistance of microbes to nanoparticles have been reported. Efflux pumps, biofilm formation/adaptation, electrostatic repulsion, alterations of morphology and mutations are some of the reported microbial resistance mechanisms to

Table 3 Nanocomposites/combined nanoparticles and their antimicrobial activity and other key finding (cytotoxic activity and mechanisms)

Nps	Method of synthesis	Shape and size	Bacteria isolates tested	Antibacterial activity (ZD/ MIC/MBC) and other key findings	Reference
Biopolymer-Ni, Zn Nps bio-composite	Biosynthesized using <i>Rhodotorula mucilaginosa</i> UANL-001L exopolysaccharide	Polymorphic arrangement without definite shape 8–26 nm	Resistant strains <i>S. aureus</i> <i>P. aeruginosa</i>	Ni-EPS Showed antimicrobial and antibiofilm activity against the two pathogens at 3 and 2 mg/ml respectively Zn-EPS also showed activity against resistant <i>S. aureus</i> at 1 mg/ml Cytotoxicity: no toxicity, as renal function showed no differences between treatments and control in vivo assays with male rat tests in the study at a concentration of 24 mg/kg of body weight	Garza-Cervantees et al. (2019)
AgNps/ZnONps	Aqueous extract of <i>Ulva fasciata</i> alga	AgNps: spherical, 15 ± 0.55 nm ZnONps: rod-shape, 187 ± 0.5 nm	<i>S. aureus</i> <i>Salmonella enterica</i> sub sp. <i>Bukuru</i> <i>E. coli</i>	Both had increased antibacterial activity with an increase in concentration against <i>E. coli</i> and <i>Salmonella</i> spp. Both demonstrated a good synergistic effect with antibiotics	Abo-Shama et al. (2020)
Tungsten carbide (Wc), silver (Ag) and copper (Cu) in combination	Commercially obtained	Wc: hexagonal with average diameter of 250 nm AgNps: rod shape, 80–90 nm CuNps: 10–20 nm	<i>S. aureus</i> <i>P. aeruginosa</i>	Significant antimicrobial activity	Bankier et al. (2019)
Ag/TiO ₂	Horizontal vapor phase growth (HVPG) technique	Nanorods geometrical shape 24.8 μm–0.22 nm	<i>S. aureus</i>	Sharp-end nanorods can eradicate bacteria with > 50% efficiency Mechanism: nanorods eliminate bacteria because of their geometrical shape-sharp ends. Sharp-end nanorods with optimal geometrical shape can naturally pierce the cell membrane of bacteria leading to shrinking. This shows that bacteria can be killed not only by the release of ions from Nps but by the ability of utilizing the shape of Nps in killing them	Muflikhun et al. (2019)

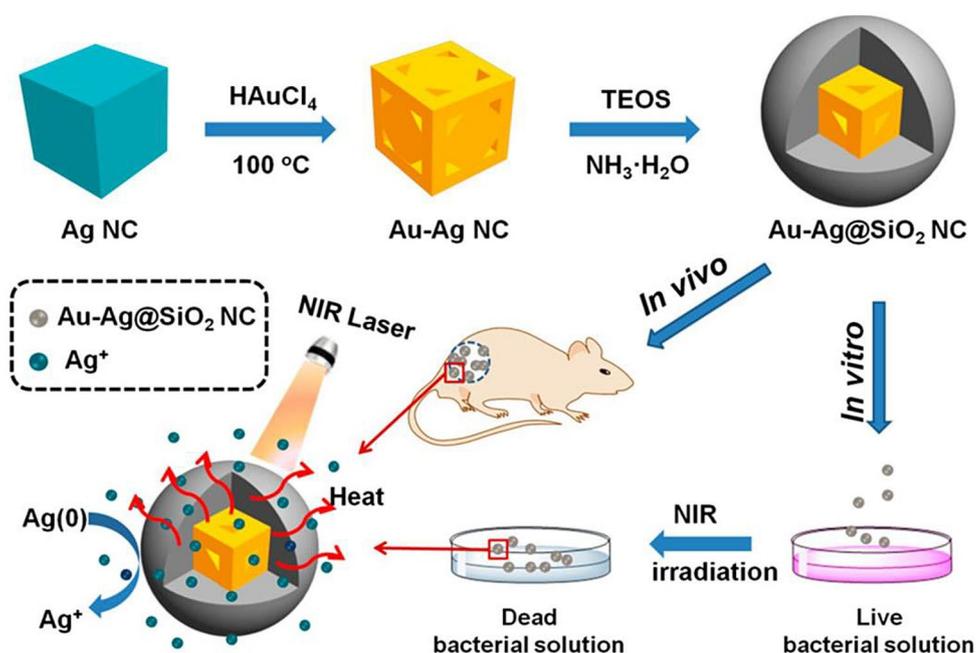
Table 3 (continued)

Nps	Method of synthesis	Shape and size	Bacteria isolates tested	Antibacterial activity (IZD/MIC/MBC) and other key findings	Reference
Ag-Au/ZnO nanostructure	Justicis adhatoda plant extract	Nano stick shape 20–25 nm	<i>E. coli</i> <i>S. aureus</i>	Good antimicrobial activity	Pandiyan et al. (2019)
α -BiO ₂ -ZnO nanostructure	Chemical synthesis	Monoclinic and hexagonal wurtzite	<i>S. aureus</i>	1.5 cm IZD for 1 mg/l	Chauhan et al. (2019)
T- β -D-glu-ZnONps (Trichoderma- β -D-glucan-zinc oxide nanoparticles)	Fungal mycellial water extract derived from <i>T. harzianum</i> (SKCGW009)	Spherical 30.34 nm	<i>S. aureus</i>	Inhibit the growth of <i>S. aureus</i> inside of roundworm and enhanced growth of roundworm Cytotoxicity: not toxic to NIH3T3 cells Exhibited the dose-dependent inhibitory effect to human pulmonary Carcinoma A549 cells IC50 of T-ZnONps and T- β -D-glu-ZnONps against A549 cells was 158 and 56.25 μ g/ml respectively	Saravanakumar et al. (2020)
ZnO/Fe ₃ O ₄ /rGO nanocomposites	Hydrothermal method	Hexagonal wurtzite Inverse spinal structure Rod-shaped morphology Spherical-shaped morphology	<i>E. coli</i> <i>S. aureus</i>	Better cidal effect on <i>E. coli</i> when compared to <i>S. aureus</i> after treatment with 1 mg/ml concentration Addition of rGO intensified antibacterial effect to a great extent	Rajan et al. (2019)
Ag/TiO ₂	Aqueous extract of <i>Acacia nilotica</i>	Spherical 20–40 nm	<i>E. coli</i> , MRSA, <i>P. aeruginosa</i>	IZD of 24, 20 and 15 mm respectively Maximum IZD was shown at 500 μ g/ml concentration. MIC was found to be 64 μ g/ml against <i>E. coli</i> and <i>S. aureus</i> while 128 μ g/ml against <i>P. aeruginosa</i> Mechanism: Decrease in the level of glutathione, triggered ROS production and lipid peroxidation	Rao et al. (2019)

Table 3 (continued)

Nps	Method of synthesis	Shape and size	Bacteria isolates tested	Antibacterial activity (IZD/MIC/MBC) and other key findings	Reference
ZEO-AgNps, ZEO-CuNps and ZEO-ZnNps (silver, copper and zinc zeolite nanocomposites)	–	Spherical 3–15 nm	<i>Vibrio cholera</i>	Each nanocomposite type had a distinctive antimicrobial effect altering each <i>V. cholera</i> lifestyle differently. Exhibit antimicrobial and antibiofilm activity Mechanisms: modification of the relative expression of genes that plays a role in biofilm formation Alteration in the level of outer membrane proteins (OmpT, OmpA, OmpU and OmpW)	Meza-vilhezcas et al. (2019)
Copper-doped chitosan-gelatin (CSG) nanocomposite coatings (Cu-doped CSG nanocomposite coating)	Green synthesis		<i>E. coli</i> <i>S. aureus</i>	Antibacterial activity was dependent on Cu concentration Cytocompatibility assessment in vitro showed that the activities of bone marrow stromal cells were not impaired on Cu-doped coatings Improved biological performance of Ti-based materials	Huang et al. (2020)

Fig. 2 Silica-coated gold-silver nanocages (Au–Ag NCs) showing antibacterial activity by a photothermal effect. Reproduced from Wu et al. (2019) with permission



nanoparticles as reported by Nino-Martinez et al. (2019) in a review.

Previously it was shown by Li et al. (1997) that the down regulation of genes coding for the porin proteins causes a decrease in nanoparticle penetration into the cell. Jordan et al. (2008) showed that the presence of envelop stress response (ESR) mechanisms help to maintain bacterial membrane integrity, reducing their interaction with positively charged nanoparticles and alterations of lipopolysaccharide (LPS) and its constituents. In a subsequent investigation by Li et al. (2010) it was also reported that the oxidation and interaction of nanoparticles with organic matters influence its antimicrobial activity. Further investigation by Hachicho et al. (2014) revealed that *P. aeruginosa* exposed to nanoparticles altered its membrane unsaturated fatty acid composition. This alteration causes a change in membrane fluidity making it difficult for the nanoparticles to enter the cell. Graves et al. (2015) also reported that the exposure of microbes to non-lethal concentration of nanoparticles can facilitate the increase in resistance due to the development of mutations that lead to the upregulation and downregulation of many genes.

The upregulation of RND and CDF transporters, P-type ATPase efflux complexes, *czcABC* and RND family efflux system was also reported as the resistant mechanism of *P. aeruginosa* exposed to different concentrations of CuONps (Yang et al. 2012; Guo et al. 2017). Other reported mechanisms of bacterial resistance to nanoparticles include, enzymatic transformation of nanoparticles (Palomo-Siguero et al. 2016), biofilm formation/adaptation (Wang et al. 2016), electrostatic repulsion (Abbaszadegan et al. 2015;

Nabavizadeh et al. 2017), pigment production (Ellis et al. 2018), and formation of biomolecule corona around the nanoparticles (Siemer et al. 2019). Panacek et al. (2018) showed that the production of flagellin (adhesive flagellum protein) by *E. coli* and *P. aeruginosa* provoked aggregation of nanoparticles leading to resistance. Faghihzadeh et al. (2018) reported that the production of extracellular substances by *E. coli* altered the size and zeta potential of AgNps leading to agglomeration and subsequent resistant to AgNps. Furthermore, *E. coli* exposed to sublethal concentration of ZnONps was reported to facilitate conjugative transfer of plasmids housing resistant genes (Wang et al. 2018). Qiu et al. (2015) in a similar investigation that exposed *E. coli* to TiO₂Nps, decrease in growth rate of bacteria with subsequent increase in conjugative transfer of genes coding for antibiotic resistance was also noted.

The alteration in the dissolution and release rate of nanomaterials in the biological system in addition to their interaction with the biological fluid can allow the microbes to modify and enhance their adaptation and fitness strategies. It is important to know that prolonged/widespread use of nanoparticles induces the expression of antibiotic resistant genes. Already the production of ROS is one of the key mechanisms of action of nanoparticles. The presence of ROS can lead to a decrease in porins proteins and upregulation of oxidative stress resistant genes. However, the ability of microbes to generate ROS when exposed to nanoparticles can be influenced by interaction with the host environment. The availability of oxygen and light can greatly influence ROS production (Yu et al. 2018). Under aerobic conditions ions can be released while anaerobic conditions can reduce

the chance of ions release. It was also reported by Chen et al. (2017) that exposure of microbes to AgNps under anaerobic condition decreases the antimicrobial activity of nanoparticles (Chen et al. 2017). Moreover, the alteration in environmental conditions can cause a spontaneous rise in mutation and also trigger genome plasticity which can greatly facilitate resistance to antimicrobial agents and evolutions of strains with increased fitness. Figure 3 summarizes the reported resistant mechanisms of bacteria to nanoparticles. Table 4 shows nanomaterials with photothermal activity as antibacterial agents.

In summary, nanoparticles have long been seen as potential solutions to the increasing resistance to conventional antibiotics and the evolution of multi-drug resistant bacteria. However, reports on the issue of microbial resistance to nanoparticles are gradually emerging. Its frequent clinical application raises the issue of resistance to these potential biomolecules (Barros et al. 2018; Finley et al. 2015). Future

studies should explore the possible resistance mechanisms of bacteria to nanoparticles. The major challenges in using nanoparticles as antimicrobial agents are summarized in Table 5.

Discussion

A large portion of the interest in nanomaterials in clinical practice stems from their drug delivery potential. Interestingly, the use of nanoparticles as a drug delivery system dated back to the early 1990s. Several new generation nanoparticles with new therapeutic modalities have been developed since then. Therapeutic and diagnostic nanoparticles fall under two categories: inorganic (AgNps, AuNps, CuONps, ZnONps, TiO₂Nps, MgONps, CaONps, Fe₂O₃Nps, MnO₂Nps, etc.) and organic (liposomes, polymeric NPs, micelles, solid lipid Nps (SLNs), nanostructured

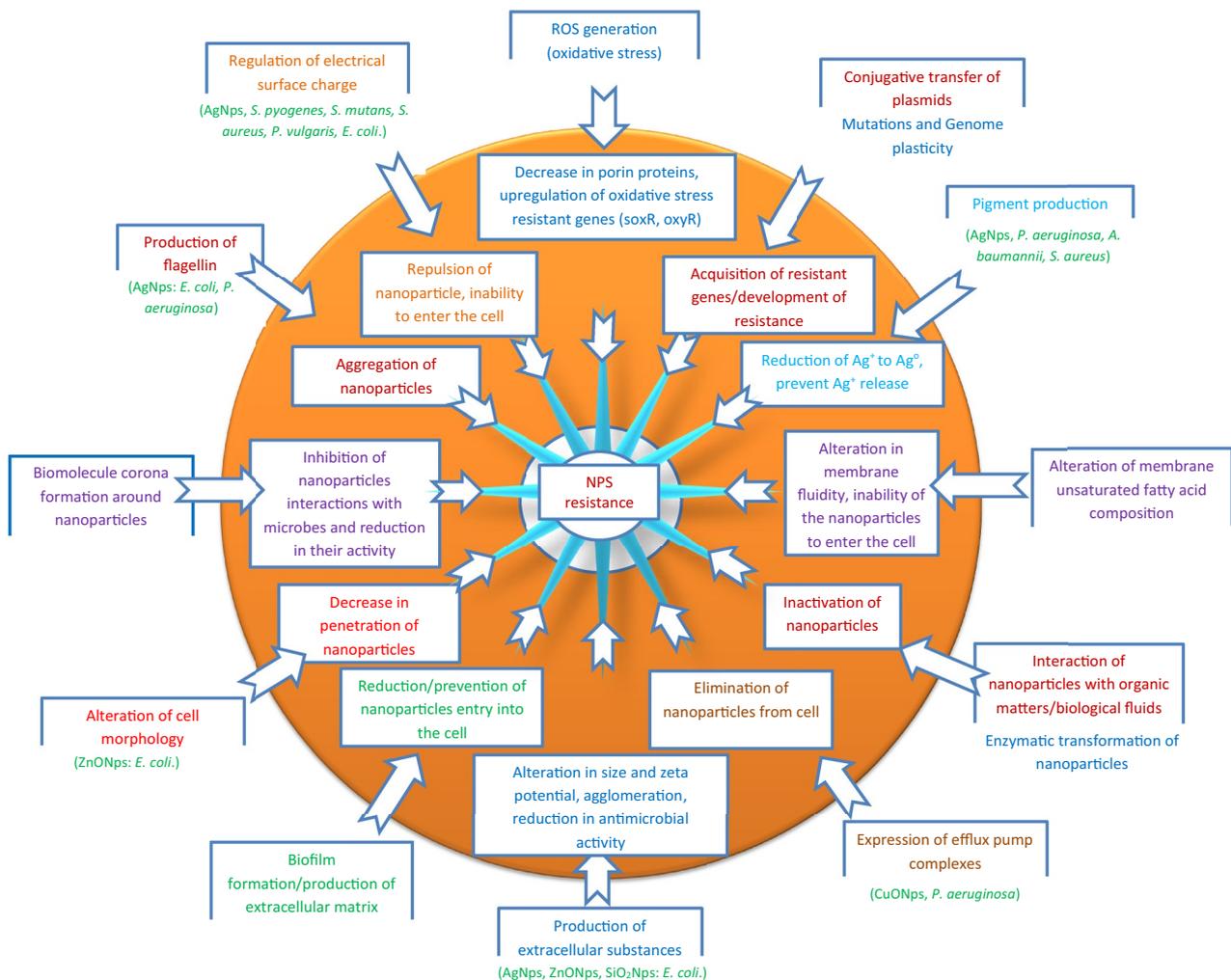


Fig. 3 Resistant mechanisms of bacteria to nanoparticles

Table 4 Nanomaterials with photothermal activity as antibacterial agents

Nanomaterials	Microbes	Size (nm)	Light wavelength (nm)	Mechanisms of antibacterial activity	References
AuNCs-DNase	Gram positive and Gram-negative bacteria		808	Disrupt biofilm and kill gram positive and Gram-negative bacteria	Xie et al. (2020)
Aniline nanogel and chitosan-containing AgNPs	<i>E. coli</i>	78	405	The release of AgNPs causes Cell membrane damage	Ballesteros et al. (2019)
AgNPs	<i>S. aureus</i> , <i>Pseudomonas aeruginosa</i>	15–20	460	In vitro investigation showed a 10-log reduction in bacterial count in biofilm In vivo study using mice showed a 100% reduction in 2 h. there was also a reduction in wound burden	Nour El Din et al. (2016)
[AL(OH)Pc(SO ₃ Na) ₄] + Au-AgNPs + aBL	<i>Pseudomonas aeruginosa</i>	14	660	There was a 3-log reduction	Maliszewska et al (2018)
AgNPs + antibiotic + aBL	<i>S. aureus</i>	15–20	460	There was a 100% reduction in bacterial growth within 8 h Excellent synergistic activity	Akram et al. (2016)
Calixarene-NO donor conjugate	<i>E. coli</i> , <i>S. aureus</i>	270	400	The release of NO causes membrane damage	Dahl et al. (1988)
PLGA NPs	<i>E. faecalis</i>	–	665	There was a 96.7% reduction in growth within 10 min	Gonzalez-Delgado et al. (2016)
CMP NPS	<i>B. subtilis</i> , <i>E. coli</i>	–	1.2 W/cm ²	For <i>B. subtilis</i> , there was a 97% reduction under 120 min while <i>E. coli</i> had a 95% reduction under 120 min	Ma et al. (2016)
AuNWs	<i>E. coli</i> , <i>S. aureus</i>	5 ± 1.5	808	Reduction of bacterial growth in vitro	Liao et al. (2020)
Ti-GNRs surface	<i>E. coli</i> , <i>P. aeruginosa</i> , <i>S. epidermidis</i> , <i>S. aureus</i>	49 ± 4 × 11 ± 2	808	Significant reduction in bacterial growth in vitro	Yang et al. (2019)
TC-AuNSs	<i>S. aureus</i> , <i>P. aeruginosa</i>	Average diameter of 120 nm	808	Reduction in bacterial growth in vitro within 5 min of exposure to NIR laser irradiation	Manivasagan et al. (2019)
PU-Au-PEG	<i>S. aureus</i> , <i>P. aeruginosa</i>	40 × 10	808	Significant reduction in bacterial adhesion in vitro and in vivo Effective photothermal killing reduction in biofilm formation	Zhao et al. (2020)

Table 5 Challenges in using nanoparticles as antimicrobial agents

S. No	Challenges	
1	Size	The size greatly influences antimicrobial potential of nanoparticles. Small size particle has a larger surface area-to-volume ratio. Parameters like synthesis method and reducing/stabilizing agents also affect the morphology, size and stability of the synthesized nanoparticles. Thus, controlling these parameters is a major challenge for efficient and highly effective nanoparticles synthesis. Nanoparticles often used as antimicrobial agents usually ranges from 1 to 100 nm. However, particle size range from 10 μ m to 10 nm are often more effective because they can easily penetrate and interact with cells. However, synthesizing nanoparticle with such size is often an issue
2	Shape	Nanoparticles are often synthesized in different shapes. AgNps for example have different shapes such as spherical, triangular or pyramid, nanorods, nanowires, flower shaped, octahedral, tetrahedral, nano-prism and nanobars. These shapes can influence the antimicrobial activity of nanoparticles
3	Aggregate	Nanoparticles can often form aggregates. The formation of these aggregates cause increase in size, thus reducing penetration into the cell and also increases toxicity
4	Biodistribution	Loss of function due to poor bioavailability is a major challenge in developing effective nanoparticle. Low retention rates of nanoparticle also reduce efficiency. Even the accumulation of nanoparticles may be detrimental to the host
5	Bioavailability	Poor dispersion affects nanoparticles activity
6	Cytotoxicity	Toxicity is a crucial issue in the use of nanomaterials. Local and systemic toxic issues in addition to being detrimental to useful bacteria in human is a major concern (Khan et al. 2016). Both nanoparticle and its degradation products can disrupt pathways involved in blood circulation due to its ability to cause hemolysis. Nanoparticle can also lead to organ dysfunction and damage. Large size nanoparticles are more toxic to the biological system than small size particles (Santos et al. 2014). The use of CuONps, ZnONps and TiO ₂ Nps is mostly limited due to their oxidative and DNA damage (Hemeg 2017). CuONps can specifically trigger hepatotoxicity and nephrotoxicity via interaction with components of the cell (Baptista et al. 2018). Although some studies have reported no significant in vivo life-threatening toxicity of nanoparticles, their accumulation could be detrimental to body cells (Zazo et al. 2016; Sengupta et al. 2014; Wei et al. 2015; Zaidi et al. 2017). Nanomaterials administered intravenously can accumulate in different organs in the body. Toxicity evaluation at the cellular and systemic levels is very crucial as it carries great clinical relevance
7	Clearance	Nanoparticles elimination from the biological system is generally low. This can lead to their prolonged accumulation in the system. The charge and size of nanoparticle greatly affect their elimination from the biological system. The kidney can eliminate some nanoparticles while those that were not degraded will be retained in the body for a prolong period of time (Lin et al. 2015)
8	Interactions	The rapid agglomeration in the use of nanoparticles is a disadvantage in their utilization as an antimicrobial agent. For example, naked ZnONps can strongly interact with organic acids in biological system which can lead to bioconjugates formation. In addition, the antimicrobial effect of nanoparticles is greatly affected by the presence of amino acids as previously stated. This protein are highly abundant in biological system and are often an issue in getting a safer product design in addition to improved product performance
9	Dosage	Dosage is major issue in nanoparticle application. Currently the dose of nanoparticles leading to disruption of cells in vitro are very high and almost not possible to use in humans. As of date, only few clinical studies are available on nanoparticles dosing. For vital therapeutic targets and reduction in toxicity, dosage optimization and evaluation is very crucial (Grumezescu 2018; Hua et al. 2018)
10	Instrumentation	High-throughput technology and equipment are also needed to manufacture nanoparticle. This often make continuous/consistent production of highly quality nanoparticle difficult
11	Scale-up/optimization	Proper guideline formulation for the production, scale-up, physiochemical property characterization, biocompatibility, standardization and protocols to draw a comparison on data origination from in vivo and in vitro experiments are lacking. Inconsistency in size, shape, morphology and other properties may also be evident during large scale production
12	Prediction	The efficiency or potency of nanomaterials is mostly very difficult to predict
13	Quality	Producing nanoparticles with uniform size and desired quality and without aggregates is also a major challenge
14	Variation in microbes and human diseases	Diversities in strains and infections caused by different microbes may influence nanoparticles activity and also complicates treatment

lipid carriers (NLCs), nanocapsules, nanotubes, quantum dots, dendrimers, emulsions, nanogels, and vesicles). Several inorganic nanoparticles have been successful in clinical studies and have been developed in the clinic for several applications (Anselmo and Mitragotri 2015). Organic

nanoparticles have frequently been used in vaccine production and as drug delivery agents. Organic nanoparticles delivered intravenously as treatments for several diseases are also available (Petros and DeSimone 2010). Organic and inorganic nanoparticles have some distinct advantages over

several intravenously administered pharmaceutical products. Compared to free drug counterparts, many organic nanoparticles can be fabricated to provide enhanced drug protection, controlled release, prolonged circulation and enhanced target to specific tissues (Wang et al. 2012). Moreover, the stimuli-responsive functions emanating from the surface plasmon resonance of inorganic nanoparticles give them an advantage over individual drugs or molecules (Torchilin 2014).

Nanomaterials have been effective against several microbes. A study by Sarwar et al. (2017) showed that ZnONPs form a complex with cholera toxin, compromises its structure, and stops its interaction with receptors present in the erythrocytes. Also, *M. tuberculosis* showed in vitro susceptibility to AgNPs (Tabaran et al. 2020), TiO₂ (Ramalingam et al. 2019), and SeNPs (Estevez et al. 2020), although their mechanism of action remains unclear. AgNPs loaded into Ti nanotubes showed promise against biofilm cells formed by MRSA. Its mechanism of action was via the release of Ag⁺ (Cheng et al. 2014b). Also, lipid-coated MSNPs loaded with colistin and conjugated with LL-37 showed activity against *P. aeruginosa*-associated pulmonary infections through isoniazid bactericidal effect (Rathnayake et al. 2020).

Moreover, it was reported that *Thymus daenensis* oil nanoemulsions were effective against bacteria causing pneumococcal infections, and its action mechanism was via oil-bacterial effect (Ghaderi et al. 2017). FA-CP-FA-coated MSNPs loaded with ampicillin were shown to be effective against *S. aureus* and *E. coli* and could be utilized in treating *S. aureus* and *E. coli*-related infections (Chen et al. 2018). Thus, nanoparticles could become an indispensable tool in the treatment of various infections. The use of nanoparticles in the treatment of both chronic and acute respiratory disease was extensively summarized in a recent article by de Menezes et al. (2021).

Also, the ability of nanoparticles to interact with different components of bacteria and exert their antimicrobial mechanisms increases with an increase in the surface/volume ratio of the nanoparticles (Azam et al. 2012). The smaller the size of the nanoparticles, the greater the surface area/volume ratio. Agnihotri et al. (2014) synthesized different AgNPs with different sizes and observed that their antibacterial effect depends on their dose and size. Studies have shown that the size of nanoparticles is one of the main factors responsible for their antibacterial activity. However, this depends on the type of synthesis, precursors, and parameters used. Size remains one of the vital factors responsible for the bactericidal effects of nanoparticles (Helmlinger et al. 2016). Nanoparticles with size < 10 nm can penetrate to the interior of the bacterial cell and exert their antibacterial effect (Khalandi et al. 2017), while that > 10 nm cannot penetrate the interior of the bacterial cell (Butler et al. 2015; Wang et al. 2011). A recent investigation by Osonga et al.

(2020) reported that the antimicrobial activities of AgNPs and AuNPs were dependent on size, with no associated toxicity. Furthermore, the surface charge of nanoparticles is also a crucial factor affecting their antimicrobial activity (Abbaszadegan et al. 2015). Moreover, the shape of nanoparticles also determines their antibacterial activity (Raza et al. 2016).

AgNPs are highly effective against bacteria. At lower doses, AgNPs show low toxicity towards humans (Shahverdi et al. 2007). Chen et al. showed that AuNPs with sizes of 8–37 nm were more toxic while AuNPs with sizes between 3 and 100 nm were less toxic (Chen et al. 2009). The toxicity was attributed to the synthesis methods and organic reducing and capping agents during the synthesis. Often, there are conflicts in findings regarding the toxic effects of nanoparticles. These differences are broadly due to a lack of standardized experimental procedures (Tao 2018). Sometimes, similar experiments lead to different conclusions. Differences in experimental techniques, doses, and administration routes have not helped the matter. This issue needs proper attention and may require a regional or international regulatory body.

Studies have shown that nanoparticles conjugated with small molecules (e.g., drugs, antibodies, antibiotics, vaccines) are usually more effective than the individual nanoparticles. The combination of nanoparticles with antibiotics greatly reduces the dosage of antibiotics to be administered. This helps to reduce toxicity associated with several antibiotics and helps to reduce resistance acquisition. Combination therapy will pave the way for nanoparticles to be used as adjuncts to existing antimicrobials; thus, helping to reduce resistance associated with most microbes. Impregnation of already available antibiotics with nanoparticles can help improve antimicrobial activity against resistant microbes. More attention should be given to synergistic interactions of nanoparticles with already available antimicrobial agents. However, it should be emphasized that the antimicrobial effect of antibiotic conjugated (impregnated) with nanoparticles depends on the antibiotics used.

Importantly, before nanoparticles can be efficiently incorporated into biological systems, clear insights regarding their stability and interaction with biological fluids (e.g., plasma, serum, proteins, lipids, electrolytes, and metabolites) are needed. The activity of nanoparticles may be influenced by their interactions with protein molecules present in biological systems. The proteins (ligands) can attach to the surface of nanomaterials and influence their dissolution, as well as their antimicrobial and cytotoxic effects. Although it has been reported that surface coating of nanoparticles could prevent their interactions with biological fluids, recent studies have proven that coating the surface of nanoparticles doesn't prevent their interaction with biological fluid nor improve their antimicrobial potential. Therefore, the interaction of nanoparticles with biological fluids is a crucial

area that needs to be exploited. Future studies should look at undesirable off-target interactions of combined nanoparticles and nanoparticles combined with antibiotics.

It is imperative to also look at the dosage of nanoparticles. Drugs that are useful at low doses may exhibit high toxicity at high doses. The doses reported in most studies vary, and the number of cells exposed is not usually reported. Future studies should look at the toxicity. Due to the promising potentials of nanoparticles, one important goal of the nanomaterials research community is to synthesize nanoparticles or nanoparticles that can conjugate very effectively at low doses (concentration). Studies should focus on non-toxic biological materials that can accelerate the potency of nanoparticles without increasing the concentration that might be toxic to biological systems. The combination of different nanoparticles can also help to reduce the dosage. Nanocomposites are also more effective than individual nanoparticles. Thus, more attention should be given to their formulation. Moreover, synthesizing nanoparticles that can bind to proteins, polysaccharides, or small bioactive compounds may be crucial in enhancing their antimicrobial potentials.

The underlying mechanism behind the activity of nanoparticles is yet to be adequately understood. The non-availability of a precise approach for in vitro analysis, in addition to the complexity of the bacterial membrane, makes it difficult to gain proper insight into the exact mechanism for antimicrobial activity of nanoparticles. To efficiently evaluate the accurate therapeutic potentials of nanoparticles and unmask the microbial response to these agents, in vivo studies are indispensable. In vivo studies are essential to elucidate their utility in biological systems fully. Therefore, further studies on the nanomaterial activity at structural, genetic, and proteomic levels are needed.

Furthermore, the frequent clinical application of nanoparticles raises the issue of resistance to these potential agents. Already, microbial resistance to nanoparticles has been summarized above. However, mutation has been one of the reported bacterial mechanisms of resistance to nanoparticles (Graves et al. 2015). Both metal and metal oxide nanoparticles seem to stimulate the co-selection and co-expression of antibiotic resistance genes. In an investigation by Wang et al. (2018), *E. coli* cultures and aquatic microbiota were exposed to sublethal concentrations of ZnONps. The exposure triggered the conjugative transfer of drug-resistance plasmids. The exposure causes an increase in the cell membrane permeability, increasing horizontal gene transfer (HGT) frequency. A similar finding was previously reported by Qiu et al. (2015), who exposed *E. coli* to a high concentration of TiO₂Nps.

It has also been reported that bacteria exposed to AgNps upregulate genes responsible for protecting against oxidative stress (*soxR*, *oxyR*, *sodB*, *sodA*) and genes responsible for converting hydrogen peroxide to oxygen (*katE* and *katG*)

(Gou et al. 2010). In their investigation, Zhang et al. (2018) showed that Al₂O₃Nps and ZnONps accelerate mutagenesis and the emergence of multiple resistance. According to the investigation, two nanoparticles increased mutation frequency and an increase in multi-antibiotic resistance in the mutation compared to the controls. The nanoparticles also enhanced intracellular ROS, leading to a rise in the frequency of antibiotic resistance mutagenesis.

Finally, photodynamic light therapy is a promising approach for treating infections, especially those due to ESKAPE pathogens. It is a minimally invasive and inexpensive approach to combat antimicrobial resistance. It is highly effective, especially in topical applications. PDT co-administered or conjugated with antibiotics, nanoparticles, antimicrobial peptides, or efflux pump inhibitors show an excellent effect. However, comparison of the efficacy of the different combinations is always difficult due to lack of standardization.

Conclusion

It is becoming obvious that nanoparticles have the potential to change clinical care by improving current therapies or introducing new therapeutic agents. For translation into clinical practice, studies on the toxicity and biocompatibility of the different combinations are needed. To date, the resistance mechanisms of microbes to nanoparticles have not been properly explored and demands adequate attention. To avoid the issue of resistance associated with conventional antibiotics, an understanding of the adaptive mechanisms of microbial resistance to nanoparticles is warranted and should be exploited in future studies. In the years to come, nanomaterials will innovate the world of technology due to their unique properties. However, one important target area of nanoparticle research should be to reduce their toxic effect on humans and enhance their bioavailability and stability.

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