Nanoparticles as New Emerging Antibacterials: Potentials and Limitations

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Abstract

The use and abuse of antimicrobials have led to the emergence of multi-drug resistant (MDR) bacteria and the spread of resistant organisms and is one of the major global threats for healthcare professionals. Alternatives to conventional antibiotics for combating resistant infections are the need of the hour. Nanotechnology-based drugs offer a ray of hope in the fight against MDR bacteria for patients as well as clinicians. Diverse types of nanomaterials have been synthesized from metallic particles with promising antibacterial activity. Efficacy of these nanomaterials depends on their interactions with bacterial cells and their mechanisms of action differ based on their physico-chemical properties. Development of novel and potent nanoantimicrobials requires in-depth knowledge of the physico-chemical properties of nanoparticles and the biological char-

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acteristics of bacteria. However, there is still a long way to go as there are major issues related to the toxicity and stability of nanoparticles. Moreover, the economic feasibility of transferring the technology from bench to bedside needs to be addressed. The present review highlights the antibacterial effects of nanoparticles, their mechanisms of action, factors affecting the activity of NPs and challenges of ongoing and future research.

Keywords
Nanoparticle · Drug resistance · MDR · Biofilm

1 Introduction

The discovery of antibiotics is considered to be one of the most significant advances in the field of medicine (Hwang et al. 2015). However, increasing drug resistance among infection-causing bacteria is slowly but surely leading to the emergence of a post-antibiotic era (Fernandes 2015). The emergence of multi-drug resistant (MDR) microbes has jeopardized the use of current antibiotic therapies (Courvalin 2016). To counter these MDR bacteria, higher doses of antibiotics are prescribed, sometimes causing toxic effects (Poulikakos et al. 2014). The treatment of drug-resistant infections has become difficult, expensive and complicated (Perez et al. 2007; Andrade et al. 2013a, b).

Drug resistance occurs naturally by selective pressure and by the horizontal transfer of resistance genes. This horizontal transfer by conjugation, transformation or transduction further worsens the situation as resistant genes disseminate to species that may be unrelated to the infection and which subsequently persist in natural environments (Doi et al. 2012; Piddock 2016). Another factor playing an important role in the inability of antibiotics to kill bacteria is the formation of biofilms by bacteria. Bacteria residing in biofilms are adhered to a surface and enclosed in a matrix of extra polymeric substances (EPS). EPS acts as a barrier against the entry of the antibiotics, making the bacteria less susceptible to antibacterial drugs. Thus, biofilm formation increases antibiotic tolerance and is a severe health threat (Husain and Ahmad 2013; Baptista et al. 2018; Jamil and Imran 2018).

Many strategies have been introduced to counter the menace of MDR bacteria in recent times and one such approach is the use of nanotechnology-developed novel nanomaterials that have different shapes and sizes and possess broad-spectrum antimicrobial action (Baptista et al. 2018). Nanoparticles (NPs) are promising candidates as they can not only demonstrate bactericidal action but can also act as carriers for conventional antibiotics and antibacterial compounds of natural origin (Wang et al. 2017). A wide range of materials have been investigated from liposomal to polymer-based nano-drug carriers. Metallic vectors, like gold NPs, are attractive core materials as they are essentially inert and non-toxic (Burygin et al. 2009). The most attractive aspect of nanoparticle-based drug delivery is the targeted delivery of various therapeutics to the site of infection effectively and safely. Drugs are delivered to the site of infection either bound to the large surface area of the NPs or

encapsulated within the NP (Gholipourmalekabadi et al. 2017). This review not only summarizes the antibacterial potential of different types of nanoparticles but also discusses various nanostructural factors that contribute to the development of potent nano-antibiotics.

2 Why Nanomaterials as Antibacterial Agents?

Materials that are typically 0.2–100 nm in size, having high surface-to-volume ratio, are termed 'nano'. These nanomaterials differ in their chemical, electrical, mechanical, optical, magnetic and electropotential properties from their bulk materials (Hajipour et al. 2012; Rudramurthy et al. 2016). Among all nanomaterials, most researches have focused on the synthesis and application of NPs. NPs are easy to synthesize, can enhance the solubility and stability of drugs and are biocompatible with target agents, and their modulated release makes them favourable candidates for use as drug vectors. The size of nanoparticles, along with their high surface-to-volume ratios, is responsible for achieving distinct functionality in drug delivery. This gives NPs an advantage over conventional therapies in the treatment of infections caused by drug-resistant bacteria (Rudramurthy et al. 2016; Gholipourmalekabadi et al. 2017). Silver nanoparticles (AgNPs) are the most studied nanomaterials and have been found to be the most effective NPs against pathogenic bacteria. However, other metal and metal oxide NPs synthesized from copper, zinc, titanium, tin, and iron have also demonstrated antibacterial potential (Dakal et al. 2016; Khan et al. 2016; Hemeg 2017; Al-Shabib et al. 2018a, b).

Conventional antibiotics suffer from poor membrane transport and thus have reduced potency (Andrade et al. 2013a, b), while NPs penetrate the membrane of host cells either by endocytosis or through interactions with surface lipids (Huang et al. 2010; Wang et al. 2017). The ability of NPs to confer physical protection against mechanisms of resistance enhances their therapeutic feasibility. Furthermore, since multiple drug combinations can be loaded into NPs, bacteria are less likely to develop resistance due to the complex mechanisms of action of different antimicrobials (Huh and Kwon 2011). However, a report on bacterial resistance against AgNPs has emerged recently (Panáček et al. 2018).

NPs demonstrate broad-spectrum bactericidal activity both against Gram-positive and Gram-negative bacteria and thus, have been employed as carriers for the delivery of antimicrobials (Rai et al. 2016; Wang et al. 2017; Zaidi et al. 2017; Hadiya et al. 2018). NPs are used as carriers because they protect antimicrobial agents from certain enzymes that either destroy or render the drug inactive. Secondly, they have the ability to deliver drugs to the target site and have the capability to carry and deliver multiple drug combinations (Huh and Kwon 2011; Rai et al. 2016; Wang et al. 2017; Zaidi et al. 2017; Hadiya et al. 2018). Moreover, NP vectors thwart pathogenic bacteria by prolonging the retention of drugs at the target site or by conjugation with the active molecules that bind a certain target (Wang et al. 2017). Conjugation of antibacterial drugs with NPs can help to overcome the therapeutic limitations of these drugs. Saha et al. (2007) demonstrated conjugation of the

antibiotics ampicillin, streptomycin and kanamycin to gold NPs, which resulted in lowered minimum inhibitory concentrations (MIC) as compared to their free drugs counterparts against both Gram-positive and Gram-negative pathogens.

3 Antibacterial Action of NPs: Mechanistic Overview

The antibacterial activity of NPs against drug-resistant pathogenic bacteria depends on a number of factors discussed above. These antibacterial effects are attributed to various mechanisms of action such as interaction with the cell wall of bacteria, inhibition of biofilm, triggering host immune response, generation of reactive oxygen species (ROS) and interaction with DNA and proteins (Fig. 1) (Hemeg 2017; Singh et al. 2017; Wang et al. 2017; Zaidi et al. 2017; Siddiqi et al. 2018).

ROS generation that induces oxidative stress is one of the key mechanisms of action of NPs against bacteria (Rudramurthy et al. 2016). Bacteria form ROS via aerobic respiration, and its production is balanced by the antioxidant systems of bacteria, but increases in ROS generation can lead to oxidation of biomolecules and cell components, leading to cell damage (Yang et al. 2012). NPs generate distinctive ROS such as superoxide (O_2^-), hydrogen peroxide (H_2O_2), which can be neutralized by endogenous antioxidants, but singlet oxygen ($^1[O_2]$) and hydroxyl radicals ($^{\cdot}OH$) cause acute death of bacteria (Wang et al. 2017). Metallic NPs demonstrate antibacterial activity as they possess high surface-to-volume ratios, and this increased ratio is usually associated with increased ROS generation, including free radicals. Several investigations on NPs have highlighted the role of ROS-mediated oxidative stress in causing the death of drug-resistant bacteria as shown in Table 1. In one study,

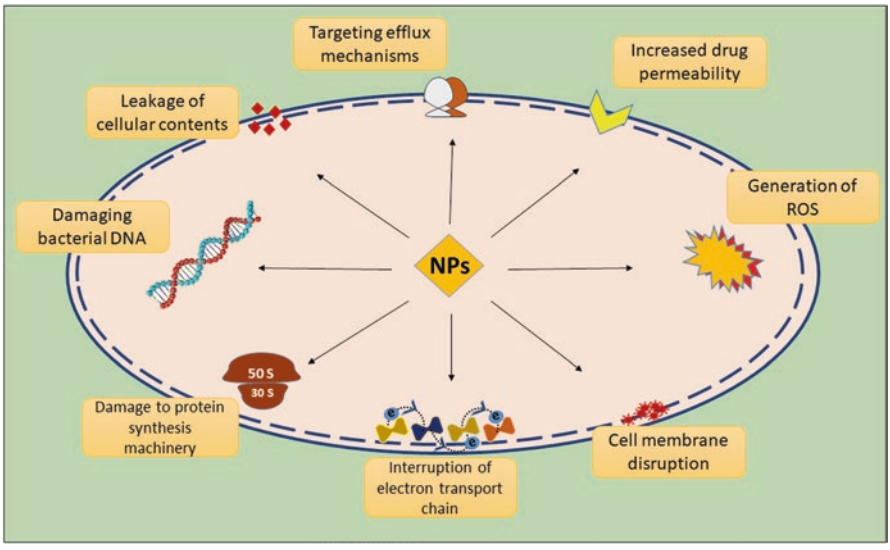

Fig. 1 Modes of action of nanoparticles in bacterial cells

Table 1 Antibacterial activity of metal and metal oxide nanoparticles and their mode of action

Drug-resistant bacterial pathogen		Active nanoparticles	Mode of action	References
Vancomycin resistant	*E. faecalis*	AgNPs	Synergistic action with vancomycin	Esmaeillou et al. (2017)
	S. aureus	AgNPs	Unknown	Saeb et al. (2014)
	S. aureus	AuNPs	Synergistic action with vancomycin	Lai et al. (2015)
	Enterococcus	Ag/Au bimetallic	Photoinactivation	Zhou et al. (2018)
Methicillin resistant	*S. aureus*	AgNPs	Synergistic action with antibiotics	Esmaeillou et al. (2017)
	S. aureus	AuNPs	ROS generation and photoinactivation	Ocsoy et al. (2017)
	S. aureus	ZnONPs	Enzyme inhibition	Cha et al. (2015)
	S. aureus	CuNPs	DNA destabilization	Kruk et al. (2015)
	S. aureus	Al_2O_3NPs	ROS-mediated cell wall disruption	Ansari et al. (2013)
	S. aureus	TiO_2NPs	Protein deactivation	Roy et al. (2010)
	S. aureus	Cu/Zn bimetallic	DNA and protein inhibition	Ashfaq et al. (2016)
	S. aureus	Graphene Oxide NPs	Generation of ROS and heat	Pan et al. (2016a, b)
	S. aureus	SiNPs	Photoinactivation	Zhou et al. (2018)
Ampicillin resistant	*E. coli*, *P. aeruginosa*	AgNPs	Synergistic action with ampicillin	Lara et al. (2010)
	E. coli, *P. aeruginosa, S. aureus*, *E. aerogenes*	AuNPs	Synergistic action with ampicillin	Brown et al. (2012)
	K. pneumoniae	ZnONPs	ROS-mediated cell wall disruption	Reddy et al., (2014a, b)
Erythromycin resistant	*E. coli*, *P. aeruginosa, S. aureus*, *E. faecalis, S. typhimurium, B. subtilis*	AgNPs	Damage to components of cell wall	Otari et al. (2013)
Teicoplanin resistant	*S. pneumoniae*	AgNPs	ROS-mediated cell death	Thapa et al. (2017)
Tetracycline resistant	*E. coli*, *S. aureus*	AgNPs	Synergistic action with tetracycline	Djafari et al. (2016)
Ofloxacin resistant	*P. aeruginosa*	AgNPs	Inhibition of efflux pump	Ding et al. (2018)

(continued)

Table 1 (continued)

Drug-resistant bacterial pathogen		Active nanoparticles	Mode of action	References
Cefotaxime resistant	*E. coli*, *K. pneumoniae*	AuNPs	Cell wall and DNA damage	Shaikh et al. 2017
Kanamycin resistant	*S. bovis, S. epidermidis, E. aerogenes*	AuNPs	Cell wall disruption	Payne et al. (2016)
Carbapenem resistant	*P. mirabilis*, *A. baumannii*	AuNPs	Osmotic imbalance, Cell wall disruption	Shaker and Shabaan (2017)
Multidrug resistant	*E. coli*	AgNPs	ROS-mediated cell death	Zhang et al. (2013a, b)
	S. aureus, Enterococcus spp., P. aeruginosa, A. baumannii	AgNPs	Physico-chemical modification of cellular components	Cavassin et al. (2015)
	P. aeruginosa, S. aureus	AgNPs	Cell wall damage	Acharya et al. (2018)
	A. baumannii	AgNPs	Affecting the permeability of cell membrane	Chang et al. (2017)
	S. aureus, *E. coli*	AgNPs	Upregulation of ATP pumps	Nagy et al. 2011
	S. aureus	AuNPs	Photo inactivation	Galanzha et al. (2012)
	E. coli	AuNPs	ROS-mediated cell death	Zhang et al. (2013a, b)
	E. coli	AuNPs	Inhibition of protein synthesis	Cui et al. (2012)
	E. coli, K. pneumoniae, E. cloacae	AuNPs	Photo inactivation	Khan et al. (2017)
	S. aureus, *E. coli*	AuNPs	Interaction with cellular biomolecules	Kim et al. (2017)
	S. aureus, *E. coli*	AuNPs	Synergism with antibiotics	Pradeepa et al. (2016)
	E. coli	ZnONPs	ROS-mediated cell death	Chakraborti et al. (2014)
	S. aureus, *E. coli*	ZnONPs	Synergism with antibiotics	Ehsan and Sajjad (2017)
	S. aureus, *E. coli*	CuONPs	ROS-mediated cell death	Singh R. et al. (2014)
	Paracoccus denitrificans	CuONPs	Modulation of nitrogen metabolism	Su et al. (2015a, b)
	P. aeruginosa	CuNPs	Hydrosol-mediated cell death	Zhang et al. (2015)

(continued)

Table 1 (continued)

Drug-resistant bacterial pathogen		Active nanoparticles	Mode of action	References
	E. coli	Fe_3O_4NPs	Membrane dysfunction	Chaurasia et al. (2016)
	S. aureus, *E. coli*, *P. aeruginosa*	Fe_3O_4NPs	Modulation of electron transfer system	El-Zowalaty et al. (2015)
	E. coli	Al_2O_3NPs	Accumulation inside the cell wall	Ansari et al. (2014)
	E. coli	TiO_2NPs	ROS generation and cell wall disruption	Li et al. (2012)
	E. coli	TiO_2NPs	Oxidation and decomposition of membrane fatty acids	Joost et al. (2015)
	E. coli	Au/Pt bimetallic	Increasing intracellular ATP levels	Zhao et al. (2014)
	P. aeruginosa	Au/ Fe_3O_4 bimetallic	Cell wall disruption	Niemirowicz et al. (2014)
	S. aureus, *E. coli*, *S. mutans*	Cu/NI bimetallic	Cell wall modulation	Argueta-Figueroa et al. (2014)
	E. coli, E. faecalis	Graphene oxide NPs	ROS-mediated cell death	Govindaraju et al. (2016)
	E. coli, P. aeruginosa, K. pneumoniae, S. aureus	Graphene oxide NPs	Multiple toxicity	Jankauskaite et al. (2016)
	S. aureus, *E. coli*	SeNPs	Cell wall disruption	Huang et al. (2017)

titanium oxide NPs (TIONPs) were shown to elicit ROS generation, causing damage to cellular components and subsequent cell death (Foster et al. 2011). In another investigation on the antibacterial action of NPs, AgNPs inhibited bacterial growth by generating superoxide and hydroxyl radicals, while the bactericidal effect of gold, nickel and silicon was attributed to the production of singlet oxygen (Zhang et al. 2013a, b). NPs made of zinc, graphene and copper have also been shown to trigger oxidative stress, leading to antibacterial effects against drug-resistant pathogens (Reddy et al. 2014a, b; Pan et al. 2016a, b; Ulloa-Ogaz et al. 2017).

Metal oxides demonstrate antibiotic action by releasing metal ions that enter the bacterial cell where they interact with the functional groups of proteins and nucleic acids. This interaction alters the structure of the cell, hinders enzymatic activity and interferes with the physiology of the bacterial cell (Wang et al. 2017). Gold functionalized superparamagnetic iron oxide nanoparticles interact with the disulphide bonds of bacterial proteins, which disrupts their metabolism and redox systems (Niemirowicz et al. 2014). In another study, Copper oxide NPs were shown to cause alteration of the expression of key proteins leading to inhibition of denitrification

(Su et al. 2015a, b). Synergy between several antibacterial mechanisms was described as the possible reason for the bactericidal effect demonstrated by the graphene oxide/Cu/Ag nano-derivatives against drug resistant Gram-negative and Gram-positive pathogens (Jankauskaitė et al. 2016).

The cell wall and membrane protect bacteria from harsh environmental conditions and foreign agents. Thus non-oxidative NP antibacterial mechanisms affect the bacterial cell wall. Structural differences in the cell wall of Gram-negative and Gram-positive bacteria make the latter more vulnerable to the action of NPs (Wang et al. 2017). In a study conducted by Ansari et al., accumulation of NPs in the cell wall resulted in the formation of pits, holes and altered metabolism, leading to cell death (Ansari et al. 2014). TiONPs were shown to inhibit growth of *E. coli* by causing membrane leakage due to increased cell volume (Joost et al. 2015). In another study carried out to investigate the efficacy of gold nanoparticles (AuNPs) against *Corynebacterium pseudotuberculosis*, Transmission electron microscopy images showed that the thick cell wall of *C. pseudotuberculosis* was penetrated by AuNPs and accumulated as agglomerates inside the cell (Mohamed et al. 2017).

4 Nano-inhibitors of Quorum Sensing and Biofilm Formation

Biofilms are aggregations of bacteria adhered on a surface, or to each other, and encapsulated in a self-made matrix of extra polymeric substances (EPS). The EPS protects the cells from the entry of antibiotics and helps to confer tolerance to bacteria (Costerton et al. 1999; Bjarnsholt 2013). NPs disrupt biofilm formation by disturbing the EPS and by interfering with bacterial quorum sensing (QS). QS is a density-dependent communication system in some bacteria that coordinates the expression of various genes including those needed for biofilm production (Rutherford et al. 2014). Since QS systems promote the formation of drug-tolerant biofilms, it is not surprising that the interference of bacterial QS and, consequently, biofilm inhibition forms the basis for the development of new age antipathogenic drugs (LaSarre and Federle 2013; Jakobsen et al. 2017; Reen et al. 2018).

Numerous reports have emerged that have demonstrated the biofilm and QS inhibitory properties of NPs of which some are listed in Table 1. Silver nanowires (SNWs) demonstrated inhibition of QS-mediated biofilm production in *Pseudomonas aeruginosa* and violacein production in *Chromobacterium violaceum* ATCC 12472 (Wagh et al. 2013). AgCl-TiO_2 nanoparticles inhibited QS-regulated production of violacein and synthesis of the QS signalling compounds, acylated homoserine lactones (AHL), in *C. violaceum* (Naik and Kowshik 2014). Lee et al. reported that ZnO nanoparticles considerably inhibited the QS-regulated production of virulence factors and biofilm formation in *P. aeruginosa* without affecting viability (Lee et al. 2014).

Vinoj et al. described the synthesis of an AHL lactonase-coated Gold nanoparticles. These nanoparticles reduced exopolysaccharide (EPS) production and consequently disturbed the biofilm architecture of the pathogen *Proteus*. This reduction in EPS and inhibition of biofilm was attributed to the increased degradation of QS

signals (Vinoj et al. 2015). Green synthesized zinc nanostructures from an extract of *Nigella sativa* seed and demonstrated broad-spectrum QS inhibition against human and food pathogens (Al-Shabib et al. 2016). In another study, ZnONPs synthesized from the leaves of *Ochradenus baccutus* reduced biofilm formation in food-associated bacteria. These NPs were found to possess no serious toxic effects even at high doses. Moreover, they were found to have excellent antioxidant properties (Al-Shabib et al. 2018c). Monophasic tin dioxide nanoflowers (TONFs) assembled by rod-like nanostructures demonstrated inhibition of QS-regulated virulence in pathogens such as *C. violaceum*, *P. aeruginosa* and *Serratia marcescens*. Significant reduction in biofilm formation in all test pathogens was also observed, which was further validated by Confocal laser scanning microscopy images illustrating disturbed biofilm architecture (Al-Shabib et al. 2018a). Recently, phytofabricated AgNPs were shown to exhibit inhibition of QS-controlled functions and biofilm formation in drug-resistant pathogenic bacteria (Hussain et al. 2019).

ROS-mediated inhibition of biofilm has also been reported for NPs. AgNPs synthesized from the leaves of *Mangifera indica* demonstrated altered biofilm architecture in *E. coli* and *S. mutans*. Interaction of AgNPs with bacterial cell walls resulted in membrane damage, ROS production and biofilm inhibition (Qayyum et al. 2017). In another study, superparamagnetic iron oxide (Fe_3O_4) nanoparticles were tested against *S. marcescens, E. coli*, *P. aeruginosa* and *Listeria monocytogenes*. Iron oxide (Fe_3O_4) nanoparticles at sub-MIC levels demonstrated broad-spectrum inhibition of biofilm in all tested bacteria. These NPs also inhibited pre-formed mature biofilms. The proposed mechanism for these effects was the interaction of NPs with bacterial cells, which generated ROS and contributed to reduced biofilm formation (Al-Shabib et al. 2018b).

5 Factors Contributing to Antibacterial Activity of Nanomaterials

Many factors govern the antibacterial efficacy of nanomaterials. These aspects need to be kept in mind when designing and synthesizing nano-antibacterials to combat drug-resistant pathogens. Some of the key factors are discussed below:

5.1 Composition and Type of Nanomaterials

Different nanomaterials display different properties against diverse classes of bacteria. Considering the case of gold nanoparticles, they demonstrate poor antibacterial properties on their own but can potentiate the efficacy of some antibiotics when they are combined. Shaikh et al. reported the synthesis of cefotaxime-conjugated gold nanoparticles that demonstrated antibacterial activity against CTX-M producing drug-resistant strains of *E. coli* and *K. pneumoniae* (Shaikh et al. 2017). Similarly, liposomes conjugated with antibiotics have high efficiency against bacteria (Drulis-Kawa and Dorotkiewicz-Jach 2010). Thus, composition of

nanoantimicrobials is an important consideration because the fundamental make-up of the material defines its surface chemistry and only the surface corona interacts with bacteria. Therefore, it is imperative to consider the composition of the nanomaterials for a specific target organism (Xie et al. 2014).

5.2 Surface Functionalization

Surface modification is performed to facilitate the passage of nanomaterials across biological barriers, but this should be done with caution as it might alter the properties of the original material. Positively charged NPs interact well with negatively charged prokaryotic surfaces, albeit with some toxicity (Thorley and Tetley 2013; Jamil and Imran 2018). Hydrophobic NPs are converted to hydrophilic ones by conjugation with polymers like polyethylene glycol (PEG) and chitosan on the surface of NPs. This process not only makes the NPs hydrophilic but also masks the host immune response and increases blood circulation time of PEGylated NPs. Hydrophobic NPs are captured by the host immune system and are not able to act against infection causing bacteria. Thus, this surface modification helps in the bioavailability of NPs (Kumari et al. 2010). Delivery of drugs encapsulated in nanocarriers to a specific site is termed targeted drug delivery. With targeted drug delivery, the site of infection receives the maximum concentration of the drug, and other organs are protected from side effects. Thus, the action of the drug will be maximized, localized and prolonged (Mahon et al. 2012; Mandal et al. 2013).

5.3 Size of Nanomaterials

Particle size is an important factor in nanotechnology, as the stability of the material depends on its size (Huh and Kwon 2011). Nanosized particles behave differently as compared to their bulk material and display size-dependent effects. As increased surface area contributes to increased activity, nanosize means more surface area is exposed and therapeutic efficacy is enhanced (Yang and Mai 2014). Guo et al. demonstrated that the activity of AgNPs increased with greater surface area, because increased surface area causes the release of more Ag^{+} leading to enhanced antibacterial activity (Guo et al. 2013).

6 From Bench to Bed Side: Clinical Application of Nano-antibacterials

Currently, few NP-based strategies are undergoing clinical trials to treat bacterial infections, probably because the high cost associated with the application of nanomaterials has limited their use as compared to conventional antibacterials. However, in case of specific clinical conditions, or high-risk patients nanobiotics may be particularly useful (Caster et al. 2017). For example, AgTive (NCT00337714) is a

silver-based catheter with improved bactericidal properties. These catheters are manufactured from polyurethanes impregnated with AgNPs. AgTive releases considerably high amounts of Ag upon interaction with body fluids and intravenous solutions to reduce blood-stream infections (Antonelli et al. 2012). Another formulation comprised of AgNPs, chitosan and fluoride was developed and demonstrated antimicrobial properties. During clinical trials, nano silver fluoride was found to be very effective as an antibacterial against *S. mutans* and *Lactobacilli* and is used to prevent dental caries in children (Dos Santos et al. 2014).

Bio-kil® (Cargico, Taiwan) is a patented nanocomposite comprised of an inorganic metal part and organic quaternary ammonium part. This is a high affinity structure and possesses a strong electric field. Bio-kil® acts by damaging the membrane proteins of bacteria through its strong electric charge. Recently, it has demonstrated efficacy against MDR and environmental bacteria in ICUs (Lee et al. 2017). Another nanoformulation called Acticoat has been used for topically against bacteria. It is nanocrystalline silver that acts by releasing Ag into wounds and is reported to inhibit biofilm formation by *P. aeruginosa* and *Acinetobacter baumannii* in vitro (Potgieter and Meidany 2018). Similarly, the efficacy of SilvaSorb (NCT00659204) is being studied at Madigan Army Medical Center and is currently in Phase III clinical trials. SilvaSorb (AcryMed, Inc., Portland) is a gel made from AgNPs and is being investigated to compare the antimicrobial efficacy of a one-time application against standard antibacterial hand gel, in reducing bacterial counts from the hands of 40 patients seeded with *S. marcescens*.

7 Challenges of Ongoing and Future Research

Research carried out across the globe has shown the great potential that nanomaterials possess for the prevention and treatment of drug-resistant infection, but transferring the technology from the lab to the clinics remains a huge challenge. Assessment of interactions between nanoantimicrobials and cells, tissue and organs, dose calibrations and administration route are some of the big hurdles that are being encountered (Sandhiya et al. 2009). Biocompatibility is another issue as most results are based on in vitro studies. In vivo studies are required to investigate the toxicity, degradability and metabolism of NPs (Beyth et al. 2015). Studies have demonstrated the accumulation of NPs injected intravenously into organs like the colon, lungs, spleen, liver and lymphatics. Inhalation of NPs can lead to cytotoxicity at various respiratory organs by systemic circulation (Hagens et al. 2007; Poma and Giorgio 2008). NPs have demonstrated hepatotoxicity and nephrotoxicity due to the free radical-mediated oxidative stress generated via interaction of NPs with bacterial cell (Jong 2008).

Although NPs hold great potential as antibiotics for the future, there are still several questions related to their acute and long-term exposure to humans that need to be addressed. Several routes of exposure (oral and gastrointestinal tract, skin, organs of the respiratory system, blood stream) need very careful consideration when examining NP exposure (Matteis 2017). Physico-chemical properties of NPs

affect their interaction with biological systems and their overall biological activity. This is well documented as various researchers have explored the anti-infection potential of metal and metal oxide NPs both in vitro and in vivo, but questions remain regarding the safety of these NPs. Compounding the problem is the vast number of different shapes, sizes, surface modifications that NPs possess; therefore, different methods are needed to evaluate their safety. Further, most studies report acute exposure rather than long-term exposure (Matteis 2017; Baptista et al. 2018; Warheit 2018). On the contrary, as research has also provided leads as to the specific mechanisms by which NPs exert toxic effects, careful surface modifications can be done to make them safe, stable and less toxic (Matteis 2017). The European Commission sponsored programmes FP7 and H2020 have helped to address concerns related to the safety of the nanoparticles (Warheit 2018). Furthermore, replacement, reduction and refinement policies related to in vivo studies have prompted regulatory agencies to realize the need for standard in vitro methodologies to establish toxicology profiles of NPs and direct labs to construct authentic and reliable databases of NPs based on their toxicological profiles. These steps will surely help in generating information on finding the right dosage at which a NP is safe for use as a therapeutic agent.

8 Conclusion

The emergence of drug resistance among pathogenic bacteria has made clinicians and researchers seek new novel drugs. In the last 10 years' nanotechnology-derived therapeutics have taken centre stage as alternatives to conventional antibiotics. Vast reports on the antibacterial activity of NPs have made it imperative to study and understand the mechanism of their action. Now there is a need for serious consideration of the critical factors related to nanostructures for successful and safe implementation as nanobiotics. Further, detailed study is required to ensure the safety of these NPs before their clinical usage. Finally, we need to understand and address the financial feasibility of transferring these nanomaterials from the lab to the clinics.

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