11 Nanoparticles: A Potential Breakthrough in Counteracting Multidrug-Resistant Bacterial Infections—A Holistic View on Underlying Mechanisms and Antibacterial Properties

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Abstract

In the present scenario, a serious predicament faced across the globe is the infection caused by bacteria. Bacterial infections rank higher among dreadful diseases and are considered to be the foremost leading causes of death worldwide. Although the recent decade has witnessed a notable development in the production of cogent antibiotics, still the efficacy of these remains questionable. Another major concern is the facile selection of antimicrobial therapy which in turn is totally empirical in nature and is often accompanied with numerous severe side effects, viz., systemic toxicity, hypersensitivity, teratogenicity, and mutagenicity. Additionally, the clinical application of antibiotics is hampered, owing to the multidrug resistance (MDR) evoked in bacteria. This further worsens up the situation and leads to a reduced therapeutic potential thereby ultimately leaving an innate effect on the public health. Apart from this, biofilm-associated infections have also significantly reduced the efficacy of currently imparted antibacterial remedial therapy, thus leaving no viable therapeutic option available. This alarming situation thus calls for the development of and designing novel alternate routes for eliminating the lacunas of the contemporary antibacterial therapeutic approach.

In this context, nanotechnology has appeared to be a pioneer, and the previous decade has seen a tremendous rise in the worldwide utilization of nanomedicines as inventive devices for battling the high rates of antibacterial resistance. Ongoing researches have demonstrated that consolidating nanoparticles with antibacterial agents additionally improves their bactericidal properties. Consolidating antibiotics with nanoparticles likewise reestablishes their capacity to kill

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microbes that have gained immunity toward them. Moreover, nanoparticles labeled with antibiotics have appeared to expand the co-localization of antibiotics at the site of the bacterium-antibiotic interaction and to encourage binding of antibiotics to bacteria. This review article will tend to highlight the physicochemical properties, mode of action, and bactericidal activity of nanoparticles in combating antibacterial resistance.

Keywords

Nanoparticles · Antibacterial · Multidrug resistance · Mechanisms · Physicochemical properties

11.1 Introduction

Recent era has witnessed a significant enhancement in the field of drug discovery and modern medicine, which has ultimately uplifted the health sector. Despite the tremendous strides being made, the researchers across the globe are facing momentous challenges when it comes to overcoming bacterial resistance (Allahverdiyev et al. 2011; Beyth et al. 2015; Wang et al. 2017). On a worldwide level, bacterial infections have been accounted for causing escalated mortality and morbidity and have proven to be a grave issue (Allahverdiyev et al. 2011; Beyth et al. 2015). Multidrug resistance (MDR) and biofilm-associated infections are some of the other factors, which have hampered the utility of present-day treatment therapies (Beyth et al. 2015).

Lately, broad-spectrum antibiotics were being employed as the first line of defense on a widespread scale for combating bacterial pathogen-based ailments. However, it became eminent that prolonged use of these antibiotics has proven to be ineffective (Wang et al. 2017). This can be ascribed to the fact that the genomic structure of these bacterial strains comprises of a super resistance gene called NDM-1 (Hsueh 2010) which facilitates them to develop an innate immunity toward active pharmaceutical formulations (Wang et al. 2017).

Antibiotics work via predominantly controlling three major mechanisms, viz., cessation of cell wall synthesis and translation and transcription (DNA replication) mechanisms (Wang et al. 2017). However, the bacteria are capable of developing resistance against any individual previously mentioned mechanisms. Apart from these, modification or degradation of antibiotic via cleaving enzymes (viz., β-lactamases and aminoglycosides) (Poole 2002) altered cellular compartmental structure (Jayaraman 2009), and evoked efflux pumps (Knetsch and Koole 2011) are some of the other prevalent factors which have resulted in the significant declination of the potency of the marketed antibiotics (Wang et al. 2017). This alarming situation, hence, calls for the development of novel alternative remedial therapies that can offer better patient compliance, reduced dosing, and effective killing of bacterial pathogens.

With the advent in science and technology, a recent field collectively coined as "nanotechnology" has emerged which has revolutionized the concept of modern-day medicine. It is by virtue of this that nanotechnology has become an imperative part of varied scientific paradigms. Nanoparticles (NPs) are sub-micron-sized colloidal suspensions having particles ranging between 1 and 100 nm in size (Farouk et al. 2018). These particles offer a narrow particle size distribution, which facilitates them with an innate ability to penetrate through the bacterial cells with certainty and ease (Farouk et al. 2018). Another illustrative property, which is of paramount importance, is their large surface to volume area ratio, which allows these particles to strongly and specifically interact with the bacterial cell wall even at smaller doses, hence resulting in an enhanced antibacterial activity (Farouk et al. 2018; Magiorakos et al. 2012). This escalated antibacterial activity can be justified based on the mode of action of NPs. As these particles tend to establish effective communication with the bacterial cell wall on one to one basis, the need for penetration is surpassed, thus viably circumventing the resistance mechanism offered by the bacteria (Farouk et al. 2018). This raises the expectation that nanoparticles would be less inclined than antibiotics to advance resistant bacteria (Beyth et al. 2015; Farouk et al. 2018). Consequently, it can be said that these nano-sized particles can act as a viable alternative to traditional antibiotic therapy for fighting bacterial afflictions (Farouk et al. 2018).

The following review article is precisely divided into four sections wherein the first section chiefly corresponds toward the introduction of the problem. In the latter part, the effect of physicochemical properties of nanoparticles on the antibacterial property has been comprehensively discussed. The present monologue also centers on defining the underlying mechanistic components of nanoparticles, which help in evading the resistance developed by bacterial pathogens. The last phase of the following manuscript pertains toward the application of the varied types of nanoparticles in mediating a theranostic approach for effective treatment of bacterial infections.

11.2 Physicochemical Properties and Invigorated Tool

In order to gain an insight into the antibacterial property of NPs, it becomes a prerequisite that the physicochemical properties of the NPs should be thoroughly investigated (Farouk et al. 2018). It has been deciphered that bactericidal properties by certain metals are possessed when they are present in their bulk forms, while other few depicts antibacterial property when they are exclusively present in nano form (Seil and Webster 2012). Thus, it can be precisely said that an individual nanoparticulate system will result in the generation of the varied types of bactericidal effect. Hence, the following section will shed some light on certain imperative and crucial factors, which tend to affect the antibacterial property of NPs (Fig. 11.1).

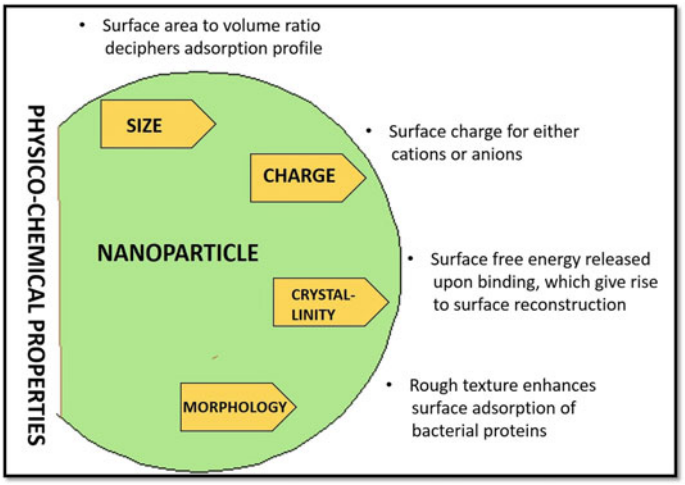

Fig. 11.1 Graphical representation showing varied physicochemical parameters of nanoparticle and their influence on the bacterial cell

11.2.1 Size/Diameter

Development of bacterial biofilms is a notable procedure, which makes these deleterious pathogens immune to traditional antibiotic treatment therapies. However, bacterial adhesion is the underlying phenomenon, which firmly substantiates the growth of these. Recent studies highlighted the fact that the size plays a notable effect on the therapeutic interventional property of the nanoparticulate system. Esfandiari et al. in a novel approach designed Ag-functionalized TiO_2 nanotubes, and the efficacy of this versatile nanostructured system was tested against *E. coli* (Esfandiari et al. 2014). The study clearly pointed toward a size-dependent bactericidal effect of the developed nanoparticulate system. It was found that the nanotubes having a smaller opening diameter (~100 nm) and AgNPs (~20 nm) produced a significantly pronounced effect than their larger counterparts.

In another study planned by Pan et al., three nano-Mg $(OH)_2$ slurries of different morphologies were utilized, and their antibacterial properties were tested on model *E. coli* bacteria (Pan et al. 2013). The fact, which came into light from this study, was the establishment of an inverse relationship between the NPs size and bactericidal effect. The smaller-sized slurries tend to have a comparatively higher antibacterial property, while a vice versa phenomenon was observed in case of larger-sized slurries. The TEM analysis showed no evidence of cellular co-localization of NPs; however, a breach in cell wall integrity was noticed (Pan et al. 2013). Both the studies clearly demarcated the importance of particle size in determining the extent and mechanism of antibacterial property. This size-dependent toxicity can be explained by the fact that a smaller-sized particle offers a greater surface area to the volume ratio. This aids in establishing an enhanced contact among the NPs and bacterial cell wall also as such smaller particles can swiftly translocate themselves

deeply into the cellular periphery of the target pathogens from the outside milieu (Deplanche et al. 2010; Gurunathan et al. 2014).

11.2.2 Morphology and Texture

Morphology or the shape of the NPs is another factor of paradigm importance, which plays an intricate role in deciding the fate of NP in inducing a bactericidal response. It became evident from the pertinent literature that NPs having a diverse spatial geometry/morphology interact with the periplasmic enzymes in a different manner. These vivid types of interactions can ultimately produce a slightly different level of damage in bacteria (Cha et al. 2015). In context to this, a study highlighted the effect of the variedly shaped nanoparticulate system on antibacterial properties (Yu et al. 2014). It was deciphered that the n-ZnO having a pyramidal geometry prevented the degradation of periplasmic enzymes. The outcomes also suggested that a photocatalytic activity was produced by these NPs and the underlying mechanism responsible for it was found to be the obstruction and reconstruction of these essential enzymes (Wang et al. 2017; Yu et al. 2014).

In a similar approach, Y_2O_3-based prismatic NPs were fabricated by Prasannakumar et al. (2015). The efficacy of these NPs in enticing a bactericidal activity was assessed in two bacterial strains, viz., *S. aureus* and *P. desmolyticum*. The study showed that the prismatic morphology of these NPs helped them to establish a strong and direct bridging with the bacterial cell wall. This interaction further resulted in the breakdown of the bacterial cell membrane, thus finally leading to cell lysis and apoptosis (Prasannakumar et al. 2015). Actis et al. studied the effect of AgNP geometry on the survival and growth rate of *S. aureus* (Actis et al. 2015). It was seen that among all the fabricated AgNPs, cubical-shaped NPs showed maximum bactericidal activity due to it its high surface area to the volume ratio and facade reactivity (Actis et al. 2015; Wang et al. 2017). Apart from the broad research in regard to the impacts of various NP attributes on bacterial cells, few investigations have highlighted the impact of texture. It has been witnessed that an increase in the roughness of the NPs surface leads to a significant enhancement in the adsorption of bacterial proteins. This escalation in the bacterial protein adsorption on the corona of NPs results in a diminished bacterial adhesion (Ben-Sasson et al. 2013; Sukhorukova et al. 2015).

11.2.3 Surface Charge Density

In recent studies, it has been repeatedly shown that the surface charge density also known as *zeta potential* has an adverse effect on the adhesive property of the NPs. The highly charged positive particles tend to attach them more firmly to the negatively charged bacterial cell wall. On the other hand, in case of negatively charged NPs, a complete paradoxical scenario is seen. This point was highlighted in a study where two types of Mg-based NPs, viz., Mg $(OH)_2$_MgCl and Mg

$(OH)_2$_$MgSO_4$, were tested for their antibacterial potential (Pan et al. 2013). The outcomes of the study demonstrated that the Mg $(OH)_2$_$MgSO_4$ NPs were readily absorbed and inbound onto the bacterial cell as compared to the Mg $(OH)_2$_MgCl NPs. This facile interaction can be ascribed based on charged moieties present on the surface of the NPs. The Mg $(OH)_2$_$MgSO_4$ had a positive charge on their corona hence were able to form ionic interactions with the charged bacterial cell wall. On the other hand, the Mg $(OH)_2$_MgCl NPs were negatively charged owing to which the electrostatic repulsive forces dominated and the NPs were unable to interact with the negatively charged bacterial cell (Pan et al. 2013).

It has also been portrayed that the accumulation of positively charged (cationic) NPs can lead to inhibited cell growth and colonization. Another factor, which came into a light, was that the abundant accumulation of cationic NPs resulted in a restricted bacterial adhesion. The abovementioned fact was corroborated by the findings of the study conducted by Fang et al. (2015). They elucidated the underlying mechanism behind the bactericidal effects produced by cationic NPs. The study pointed out that ion exchange resulted in deeper penetration of these NPs across the bacterial cell envelope, thus establishing direct communication with the cellular components. This interaction among the particles and cellular bodies was thought to be responsible for evoking a bactericidal response (Fang et al. 2015). Apart from this, it has also been hypothesized that the production of ROS entities is also significantly enhanced in the presence of positively charged NPs (Wang et al. 2017). This escalated level of ROS production finally allows the bacteria to meet their final fate, i.e., cell lysis and apoptosis.

11.3 Nanoparticles' Mode of Action for Combating Bacterial Resistance

A number of mechanisms have been proposed for elucidating the role of NPs in overcoming bacterial resistance. Among them, the first and foremost types of NPs are those which tend to display numerous modes of action in a simultaneous order (Pelgrift and Friedman 2013). The generation of these simultaneous mechanisms will prove to be highly beneficial as multiple gene mutations will be required in the same bacteria to evoke defense mechanism which is deemed to be highly unlikely possible (Blecher et al. 2011; Huh and Kwon 2011; Knetsch and Koole 2011; Schairer et al. 2012). Apart from this, another strategy, which has been seamlessly used, is the simultaneous entrapment of several antibiotics within the corona of nanoparticles and delivering the active payload cargo to the target bacterial site (Blecher et al. 2011; Zhang et al. 2010). It is a well-versed fact that a significant antibacterial activity can only be attained when direct contact between the NPs and the bacterial cell is maintained (Wang et al. 2017).

NPs possess several alluring physicochemical, biological, and mechanical properties of diverse nature, which provides them with an intrinsic ability to establish effective interaction with the target site (cell wall)/pathogens (Farouk et al. 2018). This specific interaction of NPs with the bacterial cell wall is facilitated by

electrostatic attraction, van der Waals forces, receptor ligand, and hydrophobic interactions (Armentano et al. 2014; Gao et al. 2014; Li et al. 2015; Luan et al. 2016; Wang et al. 2017). This direct interaction helps in lodging the NPs inside the cellular periphery of the bacteria where they disrupt the cellular morphology (cytosol shrinkage, cell wall rupturing, and membrane detachment) (Baranwal et al. 2018; Dakal et al. 2016). Further, they bind with the essential biomolecules (viz., DNA, RNA, protein, and lipids) and interfere with the underlying metabolic pathways ultimately resulting in altered cellular function and apoptosis (Baranwal et al. 2018; Dakal et al. 2016; Li et al. 2008; Wang et al. 2017).

The antimicrobial efficacy of nanoparticles can also be corroborated by the fact that they are capable of de-phosphorylating the tyrosine residues present in essential proteins hence modulating the signal transduction pathway (Baranwal et al. 2018; Dakal et al. 2016). Another vantage point, which came into light, was the enhancement in the permeability index of the bacterial cell, which resulted in an escalated delivery of active payload cargo. This might be ascribed to the sequence of irreversible changes occurring in the morphology of the cellular compartments owing to the interaction of NPs with a sulfur group present in cell wall proteins (Baranwal et al. 2018; Ghosh et al. 2012).

It has been deciphered that the surface charge (zeta potential) plays a key role in deciding the antibacterial efficacy of the nanoparticulate system, as it tends to govern the electrostatic interaction occurring between the NPs and bacterial cell (Farouk et al. 2018). A positive charge on the corona of the NPs allows them to interact strongly with the negatively charged cell membrane ultimately leading to disrupted cellular organelles, bacterial flocculation, and reduced survival rate (Farouk et al. 2018). Apart from these, there are certainly other mechanisms such as cessation of translation and transcription process, interrupted cell division, and cell lysis due to the production of toxic ions by NPs, which are found to be responsible for the generation of genotoxicity and cytotoxicity in bacteria (Farouk et al. 2018; Hajipour et al. 2012). The most eminent antibacterial mechanisms are as follows (Farouk et al. 2018; Hemeg 2017; Wang et al. 2017; Table 11.1).

11.3.1 Damage to the Cellular Membrane

A nonspecific mode of action is displayed by the NPs on the cellular membranes; however, an exact mechanism is yet to be discovered (Farouk et al. 2018). Nevertheless, it has been hypothesized that a certain class of cationic cyclic decapeptides commonly known as polymyxin are responsible for the antibacterial activity (Aruguete et al. 2013; Farouk et al. 2018), as they work in an orderly fashion and are responsible for disrupting the bacterial cell membrane. Another hypothesis, which has been formulated to substantiate the antibacterial efficacy of the NPs, relies upon the fact that maintenance of direct contact between NPs and bacterial cell results in an augmented cellular permeability. This further results in the formation of "voids" or hollow spaces, thus suggesting subsequent damage to the lipidic bilayer

Table 11.1 Bactericidal activity of nanoparticles

Type of NPs	Bacterial strains/cells	Proposed mode of action	Effect caused	Refs.
Interaction with cell barriers				
HAPw/n-ZnO	*S. mutans, Candida albicans, S. aureus, and E. coli*	–	Pronounced bactericidal effect in *S. mutans*, *Candida albicans*, *S. aureus* in contrast to *E. coli* Destruction of the bacterial cell membrane	Yu et al. (2014)
Nano-diamonds	*E. coli and B. subtilis*	Formation of covalent bonds with adjacent cellular matrix and intracellular proteins	Restricted enzymatic activity Disordered translation Metabolic pathways Apoptosis	Wehling et al. (2014)
TiO_2	–	Adhesion of NPs with bacterial cell wall resulted in increased membrane permeability, ROS, free hydroxyl radicals, and hydrogen peroxide production. Degradation of cell wall and cytoplasmic membrane	Intrinsic damage to the bacterial cell membrane Altered morphology Inhibited cell functions Leaked cellular (cytoplasmic) components (viz., ions and micronutrients) Apoptosis Cell lysis Complete mineralization of the organism Gradual degradation of cell wall	Foster et al. (2011) and Joost et al. (2015)
n-ZnO	*E. coli*	Adhesion of NPs with bacterial cell wall resulted in ROS production	Damaged cell membrane (honeycomb structure formation, pit, bit, or hole formation) Restricted enzymatic activity Leakage of intracellular protein	Padmavathy and Vijayaraghavan (2011)

(continued)

Table 11.1 (continued)

Type of NPs	Bacterial strains/cells	Proposed mode of action	Effect caused	Refs.
			Cell lysis and apoptosis	
Fe_2O_3 and TiO_2	*E. coli* and *S. aureus*	Inactivation of bacteria due to compression	Decomposition of bacterial cell Aggregation of bacterial cells	Zhukova (2015)
Graphene nanosheets	*E. coli*	Inactivation of bacteria due to the destructive extraction of molecular components of the cells (viz., phospholipids)	Degradation of cellular membrane	
Nano-TiO_2 (anatase)-based thin films	*E. coli*	Inactivation of bacterial cells	Enlargement in cellular structure Disruption of cellular membrane Leakage of cytoplasmic content Alteration in the chemical composition of cellular organelles Lipid peroxidation and decomposition of membrane fatty acids Cell death	Joost et al. (2015)
Al_2O_3	*E. coli*	NPs interact with cellular membrane LPS via hydrogen bonding and ligand exchange	Pits of irregular shape are formed Alteration in the level of cellular phospholipids contents Cellular membrane perforation Disruption of cellular membrane Leakage of cytoplasmic content	Ansari et al. (2014)
Diffusion				
Graphene/ iron oxide	MSRA	Diffusion of NPs inside the bacterial cell membrane resulted in the	Inactivation of bacterium due to localized heat and	Pan et al. (2016)

(continued)

Table 11.1 (continued)

Type of NPs	Bacterial strains/cells	Proposed mode of action	Effect caused	Refs.
		large-scale generation of ROS and hydroxyl radicals	oxidative stress Apoptosis	
Uncoated Ag, Au, Nic, and Si	*E. coli*	Diffusion leads to the production of superoxide (AgNPs), hydroxyl radicals (au and Ni), and singlet oxygen (Si NPs)	Altered cell membrane permeability and accumulation of generated toxic enmities resulted in bactericidal killing	Zhang et al. (2013)
Adsorption				
ZnO	*E. coli*	Zinc ion interaction with the -SH protein groups results in the generation of ROS	Disorganization of morphological symmetry of cell membrane Disruption of cellular functions Dispersed cell membranes Leakage of intra/ intercellular proteins Formation of "pits" Destroyed cellular membrane permeability Depresses enzymatic activity of cellular membrane Apoptosis	Padmavathy and Vijayaraghavan (2011)
Inhibited translation and transcription				
TiO_2	*E. coli* and K 12 cells	NPs integrated specifically with G-C rich DNA	Compression of bacterial DNA Degeneration and fragmentation of nucleic acids Diminished gene expression	Iram et al. (2015) and Zhukova (2015)
Ag	*E. coli, S. aureus*	Upregulation of antioxidant transporter and efflux pumps coding genes	Sterilization and inhibited growth Collapsed antioxidant potential	Nagy et al. (2011)

(continued)

Table 11.1 (continued)

Type of NPs	Bacterial strains/cells	Proposed mode of action	Effect caused	Refs.
Au-SPIONs	*P. aeruginosa*	NPs interact via establishing an S-S bonding with cellular membrane proteins	Disturbed cellular metabolism Inhibited redox systems	Niemirowicz et al. (2014)
SPIONs	–	ROS and superoxide production, hydroxyl radical formation, oxidative stress, catabolism of carbon source and generation of nicotinamide adenine dinucleotide (NAD)	Damaged cellular macromolecules (nucleic acids and proteins) Death of residual bacteria Lipid peroxidation	Bajpai and Gupta (2011), Durmus et al. (2012), Hajipour et al. (2012), and Leuba et al. (2013)
Suppressed metabolic gene expression				
TiO_2	C3H10T1/2 cells and *S. epidermidis*	Physicochemical properties (elevated coronal texture and subordinate water contact angle) and chemical constituents (presence of oxygen and fluorine in significantly higher levels)	Diminished adhesion and colonization (inhibited growth) of pathogens on NPs Escalated adhesion of C3H10T1/2 cells on NPs Decreased biofilm formation	Peng et al. (2013) and Roguska et al. (2015)
OSM-2	*Lactococcus*	–	Increased metabolic profiles Altered bacterial colonization Enhanced acetogenesis and methanogenesis due to an enhancement in the growth of acetogenic bacteria and archaebacteria Reduced biofilm formation	Pan et al. (2015)

cell membrane eventually leading to loss of plasma membrane (Farouk et al. 2018; Leroueil et al. 2007; Niskanen et al. 2010).

11.3.2 Production of Toxic Ions by Metallic NPs

Recently a tremendous zeal has been witnessed, where a large-scale development and application of metallic nanoparticles are taking place for eradicating the grave issue of bacterial infections. It has been deciphered that on coming in direct contact with the bacterial proteins the metallic NPs results in the formation of sparingly soluble metal ions, viz., Ag^{2+}, Zn^{2+}, and Cd^{2+} (Farouk et al. 2018). These metal ions are considered competent enough to evoke a toxic response in bacterial strains. This can be explained by taking an example of silver NPs where lodging of these NPs into the bacterial cellular periphery results in the precipitation of $AgCl^{-}$ in the cytoplasm, thus resulting in an inhibited respiration and ultimately apoptosis (Farouk et al. 2018; Niskanen et al. 2010). Degradation of the metallic NPs results in a gradual and consistent release of metal ions, which are readily absorbed by the bacterial cells. These absorbed ions establish a bridging with the functional groups (viz., amino (-NH), mercapto (-SH), carboxylic (-COOH)) of proteins and nucleic acids present in the cellular organelles (Wang et al. 2017). Disturbed enzymatic activity, altered cellular compartmental morphology, inhibited physiological and metabolic processes, and diminished survival rate are some of the utmost consequences, which are faced by the bacterial cell, which have encountered such metallic ions (Wang et al. 2017).

11.3.3 Oxidative Stress (ROS Generation)

Amid all known anti-oxidizing agents, oxygen is considered the most powerful one. Repeatedly, it has been demonstrated that during the process of respiration it acts as an efficient electron acceptor and hence can prove to be a critical factor in governing the survival rate of bacteria (Farouk et al. 2018). Oxygen can exist in varied states such as singlet, doublet, or triplet; however, it has been shown that both singlet (O_2) and triplet ($3O_2$) oxygen can prove to be toxic for cells and bacteria, respectively (Farouk et al. 2018). Peroxidation of lipidic bilayer membrane and precipitation of intra/intercellular proteins are one of the most significant effects that are produced on the generation of singlet oxygen. This finally results in the disruption of bacterial cellular compartments and ultimately killing of bacteria (Bronshtein et al. 2006; Farouk et al. 2018). Oxygen in the singlet state is the major deriving source for catalyzing several detrimental and unstructured oxidation processes taking place inside the bacterial cell.

However, during the respiratory cycle, consumption of singlet oxygen molecules by the bacterial cells results in the formation of free radicals (hydrogen peroxide activity). These generated free radicals exert oxidative stress on the nucleic acids, proteins, and lipidic bilayer membrane, thus making it difficult for the bacteria to

sustain (Bronshtein et al. 2006). It became apparent from studies that interaction taking place between DNA and bacterial cells is greatly affected by ROS production (Pramanik et al. 2012). Further, evidence corroborated the fact that ROS play an intricate role in deciding the fate of the bacteria's survival (Wang et al. 2017). This might be attributed to the fact that ROS tend to escalate the gene expression levels of oxidative proteins, which further governs the bacterial cell apoptosis mechanism (Wu et al. 2011).

11.3.4 Non-oxidative Mechanisms

In the course of time, researchers have utilized varied state of the art analytical techniques (viz., electron spin resonance (ESR), liquid chromatography-mass spectrometry (LC-MS)) in conjugation with imaging and spectroscopic analytical techniques (viz., transmission electron microscopy (TEM) and Fourier transform infrared (FT-IR)). They also utilized flat cultivation method in accordance with proteomic tools to decipher the antibacterial activity of metallic (MgO) NPs on *E. coli* (Leung et al. 2014; Wang et al. 2017). The experiment was conducted under three different light conditions, viz., UV, natural, and dark conditions. The outcome of the study clearly depicted that the incubation of NPs resulted in three vital phenomena (Leung et al. 2014; Wang et al. 2017):

1. The energy dispersive X-ray (EDX) spectra clearly outnumbered the presence of any MgO ion inside the periphery of the bacterial cell. Subsequently, TEM analysis revealed the emergence of "pores" on the palisade region along with disrupted and deformed cellular compartmental morphology.
2. A miniscule amount of generated ROS was detected by metallic NPs.
3. Negligible changes in the level of cell wall constituents (viz., lipopolysaccharide (LPS) and phosphatidylethanolamine (PE)) were observed on tearing the bacteria with the prepared NPs.

On the premises of these outrageous results, it can be summed up that MgO NP treatments did not result in any sort of escalation in the lipid peroxidation or ROS-associated protein production. However, these NPs resulted in a significant decline in the levels of several cellular metabolomic processes, which had an innate relationship with the essential regulatory processes of cell replication, lysis growth, and division (Leung et al. 2014; Wang et al. 2017).

11.3.5 Mutation in Bacterial DNA

It came into being from varied studies that metallic ions produced because of dissociation of NPs establish a facile interaction with the nucleic acid of microbes. This interaction results in the termination of transcription and cell division cycle (Dakal et al. 2016; Durán et al. 2016). This can be attributed to the fact that these

metallic ions so formed are intercalated between the DNA base pairs of the bacterial genome, thus resulting in a mutation and ultimately bacterial cell death (Hemeg 2017). In this context, studies were conducted where the antibacterial effect of metallic nanoparticles, viz., AgNPs and CuNPs, were assessed (Chatterjee et al. 2014; Dakal et al. 2016; Durán et al. 2016; Yoon et al. 2007). The study clearly depicted that AgNPs were capable of inhibiting the cell division and DNA replication, whereas CuNPs on coming in contact with the bacterial cell resulted in the degradation of bacterial DNA (Hemeg 2017). In a different experiment, a combinatorial approach employing both X-ray irradiations and BiNPs was used as potent vectors for antibacterial activity. The study pointed toward an efficient killing of the pathogen bacterial population. The exact mechanism behind this vicious killing was found to be the generation of free radicals, which brought intricate damage to the nucleic acid component (viz., DNA) of the bacterial genome (Hemeg 2017; Lellouche et al. 2012a).

11.3.6 Adsorption of Nanoparticles in Bacterial Cells (NP Interaction With Cell Barrier)

The level of toxicity of NPs is greatly governed by the electrostatic or charged interactions occurring between the NPs and the bacterial cell surface. It has been noted that a positively charged particle tends to establish much-enhanced cytotoxicity as compared to its negatively charged counterparts (Hemeg 2017). Keeping this point in consideration, surface-engineered TIO_2 NPs (AgNP-impregnated N-doped titania) were prepared by Wong et al. (2015). It was deciphered that the prepared NPs were able to establish an effective bridging, and they were readily absorbed into the bacterial cell surface. The study also pointed out that this swift translocation of NPs on the cellular surface resulted in enhanced cytotoxicity. The major mechanism behind this toxicity generation in the bacterial cell was found to be the initiation of redox reactions, which further lead to an escalation in the oxidative stress levels. Damage to bilayer lipidic membrane and intracellular proteins were some other detrimental effects, which originated due to the adhesion of these metallic particles (Hemeg 2017; Wong et al. 2015).

11.3.7 Altered Bacterial Membrane Permeability

In a series of studies, researchers prepared polyvinyl alcohol (PVA)-stabilized AgNPs (Dakal et al. 2016; Durán et al. 2016; Hemeg 2017; Sirelkhatim et al. 2015). The outcomes of the study clearly demarcated that the metallic ions thus formed adhere to the charged lipopolysaccharide membrane. This results in altered cellular membrane permeability and a subsequently enhanced ROS level production. Further, it was noticed that these factors lead to an alteration in the viscosity of the cellular membranes, thereby inhibiting and disrupting the respiratory transport mechanisms (electron transport chain, ETC) as well as electrochemical proton

gradient pump (viz., homeostatic imbalance), respectively, being operated across the bacterial cells. Disturbed physiochemical mechanisms ultimately lead to cell lysis and triggered apoptosis (Hemeg 2017). Similar results were obtained with other metallic nanoparticles as well (Chatterjee et al. 2014; Huo et al. 2016; Khashan et al. 2016; Sirelkhatim et al. 2015).

11.3.8 Cellular Envelope Permeation and Destabilization of Cellular Organelles

An effective translocation and subcellular co-localization of NPs become a prerequisite for attaining a significantly high level of cytotoxicity. However, the level of cell lysis acts as a function of zeta potential (surface charge foliage) of the NPs (Hemeg 2017). A study conducted by Lellouche et al. showed a promising application of metallic nanoparticles in apprehending the biofilm formation around catheters due to two bacterial strains, viz., *E. coli* and *S. aureus* (Lellouche et al. 2012b). In their study, they engineered the surface of catheters with MgF-NPs. The results displayed the significant antibacterial efficacy of the designed system. The surface grafted NPs were able to restrict the bacterial colonization in a comprehensive manner and offered long-lasting sterilization ability to the catheters (Lellouche et al. 2012b). The charge foliage imparted on the corona of these particles allowed them to permeate readily through the highly inaccessible cellular envelope of the bacteria. Once the NPs are lodged inside the periphery of the cell, a sudden decrease in cytoplasmic pH is observed. This drop in pH results in an escalation of the cellular membrane permeability. Owing to this peroxidation of the lipidic bilayer, membrane takes place, thus killing the bacterial colony (Hemeg 2017; Lellouche et al. 2012b).

In another study, Shamaila et al. synthesized gold nanoparticles, and the bacterial killing propensity of these NPs was tested in enteric bacterial human pathogens, viz., *E. coli*, *S. aureus*, *B. subtilis*, and *K. pneumoniae* (Hemeg 2017; Shamaila et al. 2016). It was deciphered that the proposed nanoparticulate system was capable of producing antibactericidal effects. It also came to light that the size and dose of the NPs had an innate relationship with the cellular toxicity. The mode of action of these particles was found to be the effective and deep-seated colocalization of these moieties inside the cellular organelle, viz., ribosome. This translocation facilitated the disorientation of the 30S ribosomal subunit because of which translation phenomenon was interrupted and cell lysis took place (Hemeg 2017; Shamaila et al. 2016).

11.3.9 Bacterial Film Disruption

Certain biological entities generally called as *quorum sensing molecules* are produced during the maturation phase of bacterial biofilm growth. These molecules chiefly comprise two major components, viz., matrix and carbohydrates (extracellular), which aids in establishing direct communication between the adjacent/

neighboring cells (Hemeg 2017; Neethirajan et al. 2014). The spread of bacterial infection takes place when these gradually growing bacterial cells are detached (Hemeg 2017). In lieu of this, a strategic solution has been provided by the NPs. Lellouche et al. prepared crystalline yttrium fluoride (YF_2) nanoparticles and assessed their characteristic antibacterial and anti-biofilm property (Lellouche et al. 2012a). The study pointed to size-dependent toxicity of prepared nanosystems. It was noted that smaller NPs exhibited more enhanced cytotoxicity in contrast to their bigger counterparts. The outcomes of the study revealed that an infinitesimally low concentration (mM) of NPs was able to produce a prominent cytotoxic effect in bacteria, thus retarding the growth of bacterial biofilm (Lellouche et al. 2012a). Several other research groups assessed the bactericidal effect of varied NPs (viz., Se, TiO_2, CdS, ZnO, Bi, and Ag) (Dakal et al. 2016; Dhanabalan and Gurunathan 2015; Durán et al. 2016; Guisbiers et al. 2016; Hernandez-Delgadillo et al. 2012; Lee et al. 2014; Wong et al. 2015). The outcome of the study clearly corroborated the abovementioned findings, and similar results highlighting the antibacterial targeting propensity of NPs were reported.

11.4 Bactericidal Activity of Nanoparticles

In response to the harsh environmental milieu, cell wall and membrane are the two most vital defensive parameters, which offer a protective niche to the bacteria. In other words, it can be precisely said that the exact morphology of these pathogens remains intact due to the protective coating offered by the bacterial cell wall (Wang et al. 2017). Owing to a complex physicochemical composition of the cellular membrane components, the intake of NPs generally takes place through diverse adsorption pathways in both Gram-positive (+ve) and Gram-negative (−ve) bacteria, respectively (Lesniak et al. 2013; Wang et al. 2017). In case of Gram-negative strains, the NPs are highly derived toward the bacterium, and a strong interaction among them is established.

This can be explained on the basis that numerous LPS units are exposed on the outer periphery of the cell wall, which imparts a significantly high negative charge. This in turn offers direct communication between the NPs and the host based on charge-charge interactions (Lesniak et al. 2013; Sarwar et al. 2015). On the other hand, the presence of teichoic acid on the outer corona of Gram-positive bacteria aided in widely distributing the NPs in accordance with the molecular phosphate chains across the bacterial cell wall, thereby preventing the aggregation of functional particles (Sarwar et al. 2015; Wang et al. 2017).

It became apparent from varied scientific studies that the NPs possess enhanced bactericidal effect in case of Gram-positive bacteria while in their counterpart's, viz., Gram-negative bacteria, showed comparatively lesser bacterial cell lysis/killing (Wang et al. 2017). The presence of LPS, phospholipids, and proteins across the cell wall of Gram-negative bacteria results in an altered cell morphology, thus creating a shielding barrier across the bacteria. This penetration barrier allows only

a certain group of entities to surpass through them and retards the movement of any other molecule other than macromolecules.

On the other hand, a thin layer comprising of both peptidoglycan and teichoic acid along with numerous miniscule pores is present on the cell wall of the Gram-negative bacteria. This allows the transverse passage of any foreign material swiftly through the bacterial cell, hence ultimately leading to disrupted cellular membranes and apparent cell lysis/apoptosis (Sarwar et al. 2015; Wang et al. 2017). Thus, it can be collectively said that the unique cellular composition of the vivid bacteria provides a strategic opportunity for the NPs to invade and attack the target pathogens in an efficient and comprehensive manner. Some of the studies depicting the antibacterial activity of nanoparticles are summarized in Table 11.1.

Cell membrane plays a prominent role in controlling the respiratory function of the bacteria. However, it has been depicted by ongoing studies that the respiratory mechanism of the bacterial cell membrane is highly influenced by the activity of nanoparticles (Erdem et al. 2015; Wang et al. 2017). Erdem et al. in their study evaluated the cytotoxic potential of TiO_2 NPs against two bacterial strains, viz., Gram-positive (*B. subtilis*) and Gram-negative (*E. coli*), respectively (Erdem et al. 2015). The study demonstrated an inhibited growth of bacterium due to the production of ROS entities. On the other hand, it was also deciphered that lipid peroxidation and disruption of the cellular respiratory pathway were induced owing to the presence of these NPs.

In a different study, Sondi et al. investigated the bactericidal efficacy of silver nanoparticles on Gram-negative *E. coli* (Sondi and Salopek-Sondi 2004). The treated bacterial plates were further visualized under TEM to observe the bactericidal effect of developed NPs. TEM analysis revealed the evident presence of circular pits, which signify innate damage to the bacterial cell wall, by the NP activity. Further, this resulted in escalated cellular membrane permeability and efflux of the NPs inside the cellular periphery. This resulted in an inactivated respiratory electron transport chain and lately apoptosis (Sondi and Salopek-Sondi 2004).

With recent strides in nanoparticulate therapy, another point, which came into consideration, was the bacterial cell potential. This tends to play a pivotal role in establishing direct communication between the NPs and bacterial cell, hence governing the phenomenon of apoptosis (Wang et al. 2017). A perfect example corroborating this hypothesis was demonstrated in a study conducted by Nataraj et al. (2014). They utilized fluorescence microscopy as an invigorated tool for assessing the detrimental bactericidal potential of TiO_2-based NPs on the bacterial cell membrane. It was observed that NP treatment resulted in an altered cell membrane potential which became quite apparent from the marked changes taking place in the fluoresce intensity of the cytoplasm (Nataraj et al. 2014; Wang et al. 2017).

The NPs tend to penetrate the bacterial cell wall by employing two varied penetration mechanisms, viz.:

1. *Diffusion*: The first and foremost type of penetration strategy used by the NPs is diffusion. The diffusion of nanoparticles in the bacterial cell wall or membrane is

responsible for the generation of ROS. These ROS so generated results in the inactivation of bacteria (Table 11.1).

2. *Adsorption*: Adsorption also plays an intrinsic role in controlling the bactericidal potential of NPs. The interaction of NPs with the bacterial milieu results in the fragmentation of these particles into their native ionic forms. These ions so formed tend to establish a bridging with the charged functional moieties (viz., COOH, PO_4^{3-}) situated on the palisade region of the bacterial cell. This phenomenon of adsorbing the NPs in bacterial vasculature is called *bio-sorption* (Nataraj et al. 2014). The bio-sorption process results in the lysis of cell wall and its congruent membranes, thus creating a detrimental effect on the bacterial population (Table 11.1).

Recently gradual interests of researchers have been focused on the ability of NPs to interfere with the translation and transcription mechanism, thereby altering the protein and nucleic acid synthesis phenomenology (Table 11.1). Su et al. in a study investigated the chief key mechanism responsible for the bacterial denitrification by CuO NPs (Su et al. 2015b). The detailed proteomic bio-informatic analysis revealed an alteration in the intracellular protein expressions due to the interaction of these metallic NPs with bacterial cellular components. The alteration in translational machinery resulted in the disruption of nitrogen metabolism cycle along with the inhibition of two other major cellular phenomena, viz., respiratory cycle (electron transport chain) and substance transport (Su et al. 2015b).

In an incessant attempt, Su et al. utilized varied state of the art techniques to investigate the effect of AgNPs on the translational and metabolomic profile of *E. coli*. The outcome of the study revealed that the Ag ions released from the NPs resulted in depressed enzymatic activity and inhibition of ribosomal subunit protein expression and activity of certain other proteins (Su et al. 2015b). In a similar study, Cui et al. utilized proteomic and metabolomic assays to ascertain the potency of Au NPs in evoking an antibacterial activity in Gram-negative *E. coli* bacteria (Cui et al. 2012). The study demonstrated two facile modes of action by which the NPs were able to incite a bactericidal activity in the model organism;

(a) Inhibition of bridging between ribosomal subunit and transfer ribose nucleic acid (viz., tRNA) results in disturbed protein synthesis.
(b) Alteration in the cellular membrane potential leads to depressed ATPase enzymatic activity and reduced ATP production. This ultimately results in the gross cessation of cellular activity.

The knowledge of the exact mechanism responsible for the bactericidal efficacy of NPs becomes prerequisite. Whole genome analysis is one such technique, which has equipped the present-day researcher with an ability to elucidate the antibacterial efficacy (apoptosis) in real time. A perfect example of this approach has been depicted in a study conducted by Su et al. (2015a). In their study, they utilized this

technique of paradigm importance to elucidate the mode of action of ZnO NPs on Gram-negative *E. coli*.

In addition to this, they further utilized genome-wide toxico-genomic approach on a comprehensive level to draw a comparison between the molecular response profiles of ZnO NPs and free Zn ions. The outcomes of the study indicated a wide-scale alteration in the bacterial genome, thus hindering the expression of ~387 genes. Apart from this, a significant inhibition in translation, gene expression, and RNA modification along with a demarcating alteration in the structural physiology of ribosomes was observed (Cui et al. 2012).

The normal physiological processes such as metabolism generally maintain the growth and multiplication of bacteria. A slight alteration in the metabolic processes can induce a high level of damage to the membrane and cell wall components of the bacteria. This produces a state of oxidative stress in bacteria and ultimately leads to cell lysis/apoptosis (Wang et al. 2017). It is not so that these metabolomic cycles take place individually in an isolated manner; rather, they formulate an integral part of the diverse activities taking place in a living cell. It is by virtue of this property that metabolic alterations can be used as a viable alternative to inhibit and control the growth of these deleterious microorganisms. In this context, ROS production and metal ion dissolution are the two highly claimed key mechanisms found to be responsible for the generation of an altered metabolomic process in bacteria (Table 11.1).

Leung et al. in a study utilized liquid hue spectrum analysis to probe the probable mechanism responsible for producing bactericidal effects in *E. coli* by MgO NPs (Leung et al. 2014). It was observed that the interaction of NPs with the bacterium resulted in unregulated metabolic protein expression along with the upregulated activity of both weak thiamine ester binding and riboflavin metabolic proteins. The study also pointed toward a significant downregulation of the essential mapping proteins. Owing to which, a reduction in the metabolomic activity of bacterial cells takes place, thus substantiating the hypothesis that targeting of protein by NPs can result in changed bacterial cellular metabolic profiles (Leung et al. 2014; Wang et al. 2017).

Another study reported an inhibition in the expression of a model de-nitrifier protein present in *P. denitrificans* by CuO NPs (Su et al. 2015b). An increase in the concentration of CuO NPs from 0.05 to 0.25 mg/L resulted in a diminished nitrogen removal efficiency from 98.3% to 62.1%, respectively. On further evaluation, it came to light that the facile communication of the NPs resulted in compromised surface morphology and integrity of the bacterial cells. This alteration in the cell membrane permeability allowed the swift translocation of these particles inside the vicinity of the bacterial cells. Proteomic analysis in concordance with the bioinformatics analysis further revealed unregulated expression and suppression of proteins responsible for carrying out nitrogen metabolism, electron (viz., NADH dehydrogenase and cytochrome), and substance (viz., GtsB (glucose transport)) transport. Catalytic potential and expression of nitrate and nitrite reductase enzymes were suppressed by the activity of nanoparticles (Su et al. 2015b).

The morphology of the biofilm provides an innate immunity to the bacteria making them resistant toward most of the chemical moieties (Wang et al. 2017). It has been demonstrated that the interaction of NPs with the extracellular polymeric substances (EPSs) results in altered integrity of the biofilm (Su et al. 2009). The outcome of the study conducted by Ansari et al. strongly supported the abovementioned fact (Ansari et al. 2012). In their study, it was deciphered that ZnO NPs inhibited the production of EPSs. This further amounted in generating a bactericidal activity against the biofilm of drug-resistant Gram-negative bacteria, viz., *E. coli* and *K. pneumoniae*, respectively (Ansari et al. 2012).

Another point, which came to a light, is the conduction of electrical signals by potassium ion channels across the bacterial biofilm (Lundberg et al. 2013). These ionic pumps are in turn also found to be responsible for coordinating the inter−/intracellular metabolic pathways in the bacterial biofilm. However, it was deciphered that Mg NPs can effectively and swiftly adhere and permeate through the perineum of the biofilm (Lundberg et al. 2013). This leads to a disruption in the cell membrane potential along with escalated lipid peroxidation levels and intercalation with the nucleic acid such as DNA (Lellouche et al. 2012c). Consequently, these changes in the physicochemical parameters of the bacterial cells ultimately amount to an inhibited bacterial biofilm growth and colonization (Lellouche et al. 2012c).

Salem et al. in an elaborative study deciphered the potential toxic effect of Ag and ZnO NPs on two Gram-negative bacterial strains, viz., *E. coli* and *V. cholerae* (Salem et al. 2015). The minimum inhibitory concentration (MIC) and inhibition of metabolic activity (INT) assays pointed out that a univocal amount of NPs resulted in the generation of similar bactericidal activity. It was also highlighted in the study that the NPs specifically targeted the metabolic pathways of the bacterium, which resulted in efficient apoptosis and cell lysis (Salem et al. 2015).

11.5 Conclusion

Bacterial strains impervious to the antimicrobial now being used has to turn into a genuine general medical issue that expands the need to grow new bactericidal materials. Thus, solid interest in creating novel systems or new systems can adapt to these significant issues. The rise of nanotechnology has made some new antimicrobial alternatives. Nanoparticles having varied parent compositions have exhibited gigantic potential as bactericidal agents, showing their potential as proficient antitoxin reagents in bacterial infections, wounds, and related medical issues. The adequacy of these nanoparticles changes with their physicochemical characteristics, viz., particle size, surface charge, morphology, and texture. Different nanoparticles depict bactericidal effect against various pathogenic bacterial species. Similarly, NPs have indicated adequate biocompatibility when fused in framework materials. Nanoparticles today are a promising platform for elective measures to control bacterial infections.

Antimicrobial nanoparticles offer a diversified array of classes and applications. These antimicrobial nano-sized particles offer sustained bactericidal activity with

reduced side effects, in contrast to other miniscule-sized antibacterial agents, which depicts a short-term effect and enhanced ecological toxicity. The upsurge in the number of drug-resistant bacterial strains is one of the significant issues with nanoparticulate anti-infection agents because of their particular targeting ability, though these particles physically pulverize cell films which circumvent the growth and development of these deleterious microorganisms. Because of these points of interest given by nanoparticles, endeavors have been made to utilize them in varied biomedical fields. Propelled qualitative research and development, committed endeavors, fruitful application, and commercialization of antibacterial nanoparticles will help in elevating the standard of living.

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