Chapter 12
Nanoparticles: Antimicrobial Applications and Its Prospects

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Abstract Nowadays, nanomaterials [NPs; size, 1–100 nm] have emerged as unique antimicrobial agents. Specially, several classes of antimicrobial NPs and nanosized carriers for antibiotic delivery have proven their efficacy for handling infectious diseases, including antibiotic-resistant ones, in vitro as well as in animal models, which can offer better therapy than classical drugs due to their high surface area-to-volume ratio, resulting in appearance of new mechanical, chemical, electrical, optical, magnetic, electro-optical, and magneto-optical properties, unlike from their bulk properties. Thus, scientifically NPs have been validated to be fascinating in fighting bacteria. In this chapter, we will discuss precise properties of microorganisms and their modifications among each strain specifically. The toxicity mechanisms vary from one stain to another. Even the NP's efficacy to treat against bacteria and drug-resistant bacteria and their defense mechanisms change according to strains in particular composition of cell walls, the enzymic composition, and so on. Thus, we provide an outlook on NPs in the microbial world and mechanism to overcome the drug resistance by tagging antibiotics in NPs and its future prospects for the scientific world.

Keywords Nanoparticles · Antibacterial action · Microbial resistance · NP-assisted drug delivery · Future prospects of NP-assisted therapy

12.1 Introduction

Antibacterial activity is regarded as the ability of the compounds that can kill or reduce the progression of the bacterial growth. Most of the antibacterial agents which are released in the market today are mainly either chemically synthesized or naturally extracted (Nussbaum et al. 2006). Many natural products, such as aminoglycosides, as well as purely synthetic antibiotics like sulfonamides are often used. In broad spectrum, the mediator molecules of the compounds may be either bactericidal (which kill bacteria) or bacteriostatic (slowing down bacterial growth).

There are some essential related terms for studying the antibacterial agents that are mentioned as in the following:

Terms	Explanation
Biocide	A widespread chemical or physical agent which inactivates microorganisms
Bacteriostatic	The property of a specific biocide agent which is able to bacterial multiplication
Bactericidal	A specific term referring to the property by which a biocide is able to kill bacteria
Disinfectants	Products or biocides used to reduce only the number of viable microorganisms on the inanimate objects
Septic	Characterized by the presence of pathogenic microbes in living tissue
Antiseptic	A biocide or product that inhibits the growth of microorganisms in or on living tissue
Aseptic	Free of or using methods to keep free of microorganisms. h. Antibiotics: Naturally occurring or synthetic organic compounds which inhibit or destroy selective bacteria, generally at low concentrations
Sterilization	The process where all the living microorganisms, including bacterial spores, are killed. Sterilization can be achieved by physical, chemical, and physiochemical means
Asepsis	The employment of techniques (such as usage of gloves, air filters, UV rays, etc.) to achieve microbe-free environment

12.1.1 Chemical and Physical Agents for Antimicrobial Action

The chemical and physical agents are the most widespread methods used for controlling microorganism. The physical methods include radiation, heat, and filtration which can destroy or eradicate detrimental microorganisms.

12.1.2 Radiation

Mainly there are two types of radiations, namely, ionizing and non-ionizing. Non-ionizing rays are poorly penetrating low energy rays, while ionizing rays are good penetrating high-energy rays.

Non-ionizing Rays These non-ionizing rays are with wavelength longer than the visible light. Microbicidal wavelength of UV rays lies in the range of 200–280 nm, with 260 nm being the most effective. UV rays generated from a high-pressure mercury vapor lamp produce wavelength that maximally absorbs microorganisms and causes the germicidal effect. UV rays induce formation of thymine–thymine dimers, which ultimately inhibit DNA replication. A nonlethal dose UV ray even

induces mutations in cells. The UV radiation inactivates microorganisms such as bacteria, viruses, and yeast within seconds. Since UV rays don't kill spores, they are considered to be of use in surface disinfection.

Ionizing Rays Ionizing rays, similar to the prior, are of two types, particulate and electromagnetic rays. Electron beams which are particulate in nature produce high-speed electrons by a linear accelerator from a heated cathode, while gamma rays are electromagnetic in nature and are employed to sterilize articles like syringes, gloves, dressing packs, foods, and pharmaceuticals, and sterilization can be achieved in a few seconds. Moreover, the instruments can be switched off.

12.1.3 Heat

Heat is another easier way of sterilization which exerts oxidative effects as well as denaturation and coagulation of proteins. The objects that couldn't withstand elevated temperatures can quiet be sterilized at lower temperatures by extending the interval of exposure. There are two types of heat sterilization – dry and moist heat. The dry heat deeds by protein denaturation, oxidative damage, and toxic effects of higher levels of electrolytes, while the moist heat cracks by coagulation and denaturation of proteins. Moist heat is more effective than dry heat in action as the temperature necessary to exterminate microbe by dry heat is higher than the moist heat. The minimum time required to kill a suspension of organisms at a predetermined temperature in a specified environment is known as thermal death time. In laboratory-scale cultures, a temperature of 121 °C for 15 min is utilized to kill spores. This process is called autoclaving.

12.1.4 Filtration

Filtration as the word sense just separates microbes out instead of killing them. Membrane filters with pore sizes ranging 0.2–0.45 μm are frequently used to eliminate particles from solutions that are non-autoclavable. Numerous applications of filtration contain measuring sizes of viruses, removing bacteria from ingredients of culture media, separating toxins from culture filtrates, counting preparing suspensions of viruses and phages free of bacteria, purifying hydrated fluid, and clarifying fluids. Different types of filters are earthenware filters, membrane filters, sintered glass filters, asbestos filters, as well as air filters. The additional antimicrobial agents are those chemicals which rescind pathogenic bacteria from inert surfaces (Marzieh et al. 2012).

12.2 Biological Inhibitory Mechanisms

Antibacterial properties of drugs and its essential mechanisms behind the process are very important to understand the underlying principles of its inhibitory action. Many of the bactericidal/bacteriostatic antimicrobials used currently are the ones which inhibit DNA, RNA, cell wall, or protein synthesis processes, as a result of the specific mechanistic pathways as described below:

12.2.1 Inhibition of DNA Replication by Quinolones

The processes like DNA synthesis, mRNA transcription, and cell division require the intonation of chromosomal supercoiling over strand breakage catalyzed by topo-isomerase and rejoining responses (Gellert et al. 1976; Drlica and Snyder 1978; Espeli and Marians 2004). The synthetic quinolone class of antimicrobials exploits these reactions by targeting DNA–topoisomerase complexes (Sugino et al. 1977; Gellert et al. 1977; Drlica et al. 2008). Quinolones a derivative of nalidixic acid was introduced in the 1960s to treat urinary tract infections, which was a by-product of the synthesis of chloroquine (a quinine; Hooper and Rubnstein 2003). Nalidixic acid and other first-generation quinolones (e.g., oxolinic acid) are hardly used today owing to their toxicity, whereas second (ciprofloxacin)-, third (levofloxacin)-, and fourth (gemifloxacin)-generation quinolone antibiotics (Table 12.1) are widely marketed. These can be classified on the basis of their chemical structure and of qualitative differences between the killing mechanisms they execute (Rubinstein 2001; Hooper and Rubnstein 2003).

12.2.2 The Role of Protein Expression in Quinolone-Mediated Cell Death

The double-stranded DNA breaks caused by topoisomerase inhibition by quinolones induce the DNA stress response (SOS response), where RecA is stimulated by DNA damage and encourages self-cleavage of the lexA repressor protein, persuading the expression of SOS response genes such as DNA repair enzymes (Courcelle and Hanawalt 2003) which enhances the activity of quinolones (except in the case of nalidixic acid) (Howard et al. 1993). The prevention of the activation of the SOS response has also been displayed to decrease the development of drug-resistant mutants by hindering the generation of error-prone DNA polymerases (Criz et al. 2005), horizontal transfer of drug-resistant elements (Guerin et al. 2009), and homologous recombination. Owing to these studies, illuminating the co-treatment with the protein synthesis inhibitor chloramphenicol and quinolones inhibits the ability of quinolones (Beaber et al. 2004)

Table 12.1 Some antibiotic targets and the pathways in which they effect

Drug type	Drug	Derivation	Species range	Primary target	Pathways affected
Rifamycins					
RNA synthesis, inhibitor	Rifamycins, rifampin, and rifapentine	Natural and semisynthetic forms of ansamycins (derived from *S. mediterranei*)	Gram-positive and Gram-negative species and *M. tuberculosis*	DNA-dependent, RNA polymerase	RNA transcription, DNA replication, and SOS response
β-lactams					
Cell wall synthesis, inhibitors	Penicillins (penicillin, ampicillin, oxacillin), cephalosporins (cefazolin, cefoxitin, ceftriaxone, cefepime), and carbapenems (imipenem)	Natural and semisynthetic forms of carbonyl lactam ring-containing azetidinone molecules (from *P. notatum*, *C. acremonium*, and *S. cattleya*)	Aerobic and anaerobic, Gram-positive, and Gram-negative species	Penicillin-binding proteins	Cell wall synthesis, cell, division, autolysin activity (regulated by LytSR–VncRS two-component system), SOS response, TCA cycle, Fe–S cluster synthesis, ROS formation, and envelope and redox-responsive two-component systems

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12.2.3 Inhibition of Cell Wall Synthesis: Lytic Cell Death

The bacterial cell is sheathed by strata of peptidoglycan (also known as murein), a covalently cross-linked polymer matrix that is composed of peptide-linked β-(1–4)-N-acetyl hexosamine. The mechanical strength afforded by this layer of the cell wall is crucial to a bacterium's ability to endure environmental conditions that can alter prevalent osmotic pressures; of note, the degree of peptidoglycan cross-linking compares with the structural integrity of the cell. Maintenance of the peptidoglycan layer is accomplished by the activity of transglycosylases and penicillin-binding proteins (PBPs; also known as transpeptidases), which add disaccharide pentapeptides to encompass the glycan strands of existing peptidoglycan molecules and cross-link adjacent peptide strands of immature peptidoglycan units, respectively (Bugg and Walsh 1992). The treatment with an inhibitor of cell wall syntheses changes induction of cell stress responses, cell shape and size, and ultimately cell lysis. For instance, β-lactams (including penicillins, carbapenems, and cephalosporins) wedge the cross-linking of peptidoglycan units by obstructing the peptide bond formation reaction that is catalyzed by peptidoglycan-binding proteins (PBPs) (Wise and Park 1965; Holtje 1998; Park and Uehara 2008). This inhibition is achieved by penicilloylation of the PBP active site – the β-lactam (containing a cyclic amide ring) is an analogue of the terminal d-alanyl-d-alanine dipeptide of peptidoglycan. Penicilloylation of the PBP active site blocks the hydrolysis of the bond created with the now ring-opened drug, thereby disabling the enzyme (Waxman et al. 1980; Josephine et al. 2004) through autolysis using autolysins. Autolysins are membrane-associated enzymes that break down bonds of peptidoglycan strands. Autolysins have also been displayed to show a part in lytic cell death in bacterial species that contain numerous peptidoglycan hydrolases, such as *E. coli* (Tipper and Strominger 1965). In *E. coli*, a set of putative peptidoglycan hydrolases (lytM domain factors) were shown to be important for rapid ampicillin-mediated lysis (Uehara et al. 2009). The discovery that autolysins contributed to cell death expanded our understanding of lysis and showed that active degradation of the peptidoglycan with inhibition of peptidoglycan synthesis by a β-lactam antibiotic triggers lysis.

12.2.4 Non-lytic Cell Death

Streptococcus pneumoniae lacking peptidoglycan hydrolase activity can still be killed by β-lactams, but at a slower rate than autolysin-active cells, indicating that there is a lysis-independent mode of killing induced by β-lactams (Moreillon et al. 1990; Hoch 2000; Novak et al. 2000). For instance, in *Staphylococcus aureus*, the lytSR two-component system affects cell lysis by modifying autolysin activity (Burnskill and Bayles 1996). lytR triggers the manifestation of *lrgAB*, which was found to impede autolysin activity and thereby lead to antibiotic tolerance. lrgA is similar to bacteriophage holin proteins (Groicher et al. 2000), which control the

access of autolysins to the peptidoglycan layer. Based on this evidence, a supplementary holin-like system, *cidAB*, was uncovered in *S. aureus* and initiated to activate autolysins, representing *S. aureus* more susceptible to β-lactam-mediated killing. Complementation of *cidA* into a *cidA*-null strain inverted the damage of autolysin activity but did not wholly reinstate sensitivity to β-lactams (Rice et al. 2003).

12.2.5   Role of the SOS Response in Cell Death by β-Lactams

The handling with β-lactams leads to variations in cell morphology that are accompanying with the primary drug–PBP interaction. Generally speaking, PBP1 inhibitors source cell elongation and are strong activators of lysis, PBP2 inhibitors change cell shape but do not lyse, and PBP3 inhibitors impact cell division and can persuade filamentation (Spratt 1975). Accordingly, PBP1-binding β-lactams are also the most effective inducers of peptidoglycan hydrolase activity, and PBP2 inhibitors are the least proficient autolysin activators (Kitano and Tomasz 1979).

12.2.6   Inhibition of Protein Synthesis

The mRNA translation process occurs over three sequential phases (initiation, elongation, and termination) that comprise the ribosome and a range of cytoplasmic accessory factors (Garrett 2000). The ribosome is composed of two ribonucleoprotein subunits, the 50S and 30S, which assemble (during the initiation phase) following the formation of a complex between an mRNA transcript, *N*-formylmethionine-charged aminoacyl tRNA, several initiation factors, and a free 30S subunit. Drugs that inhibit protein synthesis are among the biggest classes of antibiotics and can be divided into two subclasses: the 50S inhibitors and 30S inhibitors (Table 12.2). 50S ribosome inhibitors include lincosamides (e.g., clindamycin), macrolides (e.g., erythromycin), streptogramins (e.g., dalfopristin– quinupristin), amphenicols (e.g., chloramphenicol), and oxazolidinones (e.g., linezolid) (Nissen et al. 2000; Katz and Ashley 2005). The 50S ribosome inhibitors work by physically blocking the access of aminoacyl-tRNAs to the ribosome or either initiation of protein translation (as is the case for oxazolidinones) (Patel et al. 2001). Among ribosome inhibitors, the only class that is broadly bactericidal is naturally derived aminoglycosides. Macrolides, streptogramins, spectinomycin, tetracyclines, chloramphenicol, and macrolides are typically bacteriostatic; however, they can be bactericidal in a species- or treatment-specific manner.

Even though antibiotics can be a preventive measure for bacterial growth, to the excitement of the scientific community, they exhibit a phenomenon called microbial resistance. This results in a portent that the microbe develops survival even when antibiotics are administered after a point where which they get mutated itself and

Table 12.2 Antibiotics which affect ribosome machinery

Drug type	Drug	Derivation	Species range	Primary target	Pathways affected
Aminoglycosides and tetracyclines					
Protein synthesis inhibitors	Gentamicin, tobramycin, streptomycin, kanamycin, tetracycline, and doxycycline	Natural and semisynthetic forms of amino sugars (-mycins from *Streptomyces* spp. and -mycins from *Micromonospora* spp.)	Aerobic, Gram-positive and Gram-negative species, and *M. tuberculosis*	30S ribosome	Protein translation (mistranslation by tRNA mismatching), ETC, SOS response, TCA cycle, Fe–S cluster synthesis, ROS formation, and envelope and redox-responsive two-component systems
Macrolides					
Protein synthesis inhibitors	Erythromycin and azithromycin	Natural and semisynthetic forms of 14- and 16-membered lactone rings (from *S. erythraea* and *S. ambofaciens*)	Aerobic and anaerobic, Gram-positive and Gram-negative species	50S ribosome	Protein translation (through inhibition of elongation and translocation steps) and free tRNA depletion

Courtesy to: Nature review, Microbiology, 2010: 8: 423–435

become resistant to those antibiotics which they have come across earlier in its lifetime. Here comes the application of nanoparticles (NPs) as a carrier of antibiotics/ a replacement of antibiotics.

## 12.3	Positive Side: As an Effective Therapeutic Method to Combat Microbial Resistance and Multidrug-Resistant Mutants

Against microbial resistance and multidrug resistance (MDR), numerous NP variants and NP-based materials have been used as a new line of defense (Singh et al. 2014; Cavassin et al. 2015) having different mechanisms for compaction. The complementary advantages of using NPs/nanotechnologies as antibacterial agents compared with traditional antibiotics can be summarized as follows:

1. Overcoming the existing antibiotic resistance mechanisms including the disruption of bacterial membranes and the hindrance of biofilm formation
2. Combatting microbes using multiple mechanisms simultaneously
3. Acting as good carriers of antibiotics (Zhang et al. 2010)

### 12.3.1	Overcoming the Existing Antibiotic Resistance Mechanisms

Many NPs usually counteract at least any one of the common resistance mechanisms. These possessions are effect of the bactericidal mode of NPs, which bases on their specific physicochemical properties (Chen et al. 2014). The uniquely small size helps NPs to interact with cells due to a larger surface area-to-mass ratio with handy and manageable application, in contrast to traditional antibiotics. Besides the interruption of bacterial membranes, difficulty of biofilm formation is another significant mechanism, as they portray a major measure in the progress of bacterial resistance (Peulen and Wilkinson 2011). The distinctive structure and arrangement of bacterial biofilms deliver protection to the implanted microorganisms, assisting them to escape from most antibiotics. Moreover, bacterial biofilms are "a breeding ground" for regular resistance mutations and the interchange and variation of these mutations among diverse bacterial cells (Khameneh et al. 2016). Studies have revealed that many NPs can prevent or overcome biofilm formation, including Au-based NPs (Yu et al. 2016), NPs, 7 CuO NPs (Miao et al. 2016), Ag-based NPs (Markowska et al. 2013), ZnO Fe3O4 NPs, Mg-based NPs (Lellouche et al. 2012b), NO NPs (Hetrick et al. 2009; Slomberg et al. 2013), and YF NPs (Lellouche et al. 2012a). Better prevention of biofilms is attained by a lesser size and larger surface area-to-

mass ratio, as well as the particle shape of NPs with an extraordinary outcome on biofilm destruction (e.g., NPs with a rodlike shape are more operational than NPs with a spherical shape).

12.3.2 Combatting Microbes Using Multiple Mechanisms Simultaneously

The antimicrobial mechanism of traditional antibiotics is modest owing for bacteria to develop resistance. In disparity to traditional antibiotics, NPs combat microbes via multiple mechanisms that are simultaneously active. The advantage of these simultaneous mechanisms is that even though microbes have multiple mutated genes, Nps can assist so as to reduce the microbial resistance.

12.3.3 Acting as Good Carriers of Antibiotics

NPs not only can combat bacterial and microbial resistance themselves, as mentioned earlier, but also can act as a "medium and carrier" of antibiotics. However, the mechanisms of NP-based drug delivery are different from those presented earlier.

12.3.4 Several Types of NPs Are Currently Used for Drug Delivery

Solid lipid (SL) NPs (Thukral et al. 2014; Naseri et al. 2015), liposomal NPs (Daeihamed et al. 2017), polymer-based NPs, inorganic nanodrug carriers (including magnetic NPs, mesoporous silica NPs, polymer micelles, carbon nanomaterials, and quantum dots), dendrimer NPs (Liu et al. 2015), and terpenoid-based NPs (Abed and Couvreur 2014) are used as a transporter for the supply of antibiotics; the central advantages of NPs associated with conventional distribution systems are as follows:

Size The governable smaller size of NPs is appropriate for accompanying antimicrobial operations and fighting intracellular bacteria (Ranghar 2012). The management of infections caused by intracellular strains with drug resistance is more multifarious using antibiotics (Andrade et al. 2013; Qi et al. 2013) because of antibiotics' reduced membrane transport. Drugs of ordinary size have less influence on intracellular microbes. An improved treatment method using drug-loaded NPs as mediators has been projected to overcome the limitation.

Protection NP carriers can aid to rise the serum levels of antibiotics and shield the drugs from resistance by targeted bacteria. Within NP carriers, drugs are sheltered from harmful chemical reactions so as to maintain the potency of the drugs. Moreover, better efflux and reduced uptake of antibiotics in bacterial cells (such as in *P. aeruginosa* and *E. coli*) are the normal and significant reasons for resistance to traditional antibiotics. However, researchers have proved that numerous NPs can incredulous these mechanisms (Muhling et al. 2009), preventing drug resistance. For example, in the gastrointestinal tract, dendrimers can inhibit P-glycoprotein-mediated efflux (Liu et al. 2015).

Precision and Security NP carriers can minimize systemic side effects and target antibiotics to an infection site. When we use a carrier, we can reduce the side effects (including drug toxicity) and can encourage a high-dose drug absorption at the desired site. NP-based antibacterial drug delivery systems deliver the drug to the site of action and therefore reduce the side effects. Targeted NP-based drug delivery entails of active targeting or passive targeting. Active targeting is achieved through NPs' surface modification, allowing the NP-based drug delivery system to selectively identify precise ligands on the cells at the site of infection, while passive targeting is achieved through improved permeation and retaining at the infection site. Active targeting embraces receptor targeting, temperature targeting, and magnetic targeting (Xiong et al. 2012).

Controllability Controllable sustained discharge of antibiotics can be attained docilely. With a conventional delivery method, the blood drug level is maintained for a short time with the lowest effective dose. As a consequence, frequent dosing is obligatory, which leads to side effects. With the appropriate NP carrier or method of drug release, the blood concentration of the medicine at the infection site can be persistent at the compulsory effective level for a long time, occasioning in good stability, compact frequency of medication, enhanced patient compliance, and condensed patient pain. Along with prolonged drug release (Liu et al. 2016), Nps are effective even by different types of governable stimulatory factors (such as a magnetic field, chemical agents, light, heat, and pH) (Lim et al. 2018; Wu et al. 2016; Baig et al. 2016).

Combination Many drugs can be packaged within the same NP or with assisted constructs to increase the agents' antibacterial properties. The concurrent combination of dissimilar drugs helps in developed efficiency due to the joint action of multiple mechanisms. On the other hand, two or more types of NPs can be used in combination for improved antibacterial effects and prevention of resistance (Liu et al. 2015). Fusion NPs can maximize the powers while diminishing the weaknesses of the individual types of NPs. For example, studies have shown that superior efficacy of in vivo cellular delivery can be achieved by lipid–polymer hybrid NPs compared with delivery without polymeric NPs or by liposomes (Hadinoto et al. 2013), which can effectively and expressively decrease the possibility of the growth of bacterial resistance (Brooks and Brooks 2014). The abovementioned advantages may unite in diverse combinations with different emphases in the process of actual application.

Size The recent studies have revealed that the size of NPs has a great role in its bioactivity. The length and diameter of nanotubes were attuned by the anodic oxidation process parameter by increasing the release time of drug. The TiO2 nanotubes and silica NPs administered syneretically on the composite films for antibacterial activity resulted that the size of the TiO2 nanotubes basically dogged the amount and machinery of the activity. Smaller NPs having larger specific surface areas resulted in larger permeability to the cell membranes (Gurunathan et al. 2014; Deplanche et al. 2010).

Shape Shape also accounts for antimicrobial activity. NPs interacting with periplasmic enzymes cause varying gradations of bacterial cell damage with respect to the shape of NPs (Cha et al. 2015). A comparison of ZnO NPs with pyramid, plate, and sphere shape showed the arrangement of β-galactosidase (GAL), and shape-specific ZnO NPs produced photocatalytic activity (Prasannakumar et al. 2015). *Pseudomonas desmolyticum* and *S. aureus* were greatly affected with prismatic-shaped Y2O3 NP due to the direct interaction between NPs and the surface of the bacterial cell membrane (Hong et al. 2016). Moreover, cube-shaped AgNPs exhibit stronger antibacterial activity than sphere-shaped and wire-shaped AgNPs with similar diameters, due to the specific surface area and facet reactivity (Actis et al. 2015) having a lesser effect on microbiota susceptibility (Talebian and Sadeghi 2014).

Roughness Roughness also acts as a factor with respect to antibacterial action as the roughness of NPs increases the size and the surface area-to-mass ratio, which promotes the adsorption of bacterial proteins, followed by a reduction in bacterial adhesion (Sukhorukova et al. 2015).

Zeta Potential Recent studies have validated that the zeta potential for NPs has durable influence on bacterial adhesion. The electrostatic attraction among positively charged NPs and the bacterial negatively charged cell membrane has a positive surface charge and is prone to being adsorbed on the bacterial surface and is meticulously connected with bacteria, in contrast to their negatively charged counterparts (Pan et al. 2013), and rises vascular permeability (Maeda 2010), by limiting bacterial attachment through ion exchange (Fang et al. 2015). In comparison with negatively charged and neutral NPs, positively charged counterparts have been believed to enhance ROS production, which leads to interactions between the NPs and the bacterial surface (Arakha et al. 2015).

Doping Modification The NPs used in clinics can be now altered for its aggregation using doping modification techniques allowing NPs to disperse in hydrophilic or aqueous environments. Doping modification is also one of the most operational methods to normalize and regulate the interaction of NPs with bacteria. Lately, the ZnO NPs with Au (gold) combination to form ZnO/Au nanocomposites were administered to improve photocatalytic activity and to enhance ROS generation. These effects are the result of the following factors: an altered ZnO bandwidth, better light absorption owing to the surface plasmon resonance wavelength of Au, enhancement of the photo-induced charge carrier reactivity, and amplified electron transport efficiency and carrier charge separation (He et al. 2014). For instance, ZnO

NPs doped with fluorine generate more ROS than ZnO NPs, resulting in greater damage to bacterial cells (Guo et al. 2015; Podsporka et al. 2017). The ZnO NPs have "O" content at the surface regulating antimicrobial effectiveness against both Gram-positive and Gram-negative bacteria (Mehmood et al. 2015). Nano-TiO2 reduces the formation of biofilms in dental implants, showing greater antimicrobial action. In comparison with unmodified TiO2, nano-TiO2 increases photocatalytic activity, as the doped form can effectively extend the active spectrum to the visible light region by the valence bandwidth elevation and the forbidden bandwidth deprivation (Peng et al. 2010; Sangari et al. 2015).

Environmental Conditions Various environmental conditions displayed significant differences in antimicrobial activity. For example, the temperature of the environment potentially influences the antibacterial activity following its effect on the ROS generation rate. When ZnO NPs are encouraged by temperature, electrons are detained at the active sites. Afterward, the electrons interact with oxygen molecules (O2) for ROS generation, thereby increasing the antimicrobial effectiveness of ZnO NPs. A decrease in the pH increases the rate of dissolute ZnO NPs, which elevated the antimicrobial properties (Saliani et al. 2015). In addition, under acidic conditions, the injury of ability of poly (lactic-*co*-glycolic acid) (PLGA)-poly(l-histidine) (PLH)-poly(ethylene glycol) (PEG)-encapsulated vancomycin deceased selectively. Certain results proposed that protonation of the imidazole groups of PLH selectively under acidic conditions intensely influenced NP surface charge switching. The surfaces of the NPs were charged positively at low pH that becomes beneficial to the interaction with the negatively charged groups of the bacterial cell barrier, prompting multivalent strong electrostatic regulation (Radovic et al. 2012). Another study proposed that the interaction of Ag+ with dissolved oxygen and protons caused an oxidative dissolution mechanism for AgNPs which could activate AgNPs and release many Ag ions, enhancing the antibacterial activity of the AgNPs in acetic acid than in neutral water (Peretyazhko et al. 2014).The culture medium characteristics, such as osmotic pressure and pH, can influence the aggregation, surface charge, and solubility of NPs. Antibacterial tests in five types of media demonstrated that the antimicrobial activity of ZnO NPs is mainly due to free Zn ions and zinc complexes. Furthermore, the medium can supply nutrients to bacteria to improve their tolerance to NPs (Li et al. 2011). Finally, a study has shown that preparation of ZnO NPs under different stirring conditions can affect their antibacterial activity against Gram-positive (*B. subtilis*) and Gram-negative (*E. coli*) bacteria and a fungus (*C. albicans*; Khan et al. 2016).

12.4 Mechanism of Action of Nanoparticles

One key element in the design of a more potent antibacterial system is the understanding of its mode of action. This involves two distinctive steps – the first one is the way the system will behave in the physical or chemical modifications occurring

in environments involving aggregation, dissolution, RedOx photo-reactions, release of adsorbed silver species, adsorption or desorption of ions, molecular species or polymers, or interaction with other nanoparticles or surfaces which can all have an effect on the speciation of silver, modifying this metal availability and impacting the antibacterial effect, while in the second step, the silver-containing species interact with the bacterial cell and lead to the cellular death. This impact trusts on the considered organism, even the synthetic parameters (ligand type, shape, size, washing steps, dispersion, evaluation procedures for bacterial strain used, growth inhibition due to toxicity criterion or full eradication, nature of the test to assess it, presence of light or oxygen, composition of the medium, and so on) (Misra et al. 2012). As many modes of action are hypothesized from experiential observations and condition evaluated, several decontamination pathways analyzed for silver nanoparticles remain unclear to this date. But some of the theorized silver nanoparticle (AGNP) effects are described in detail below followed by gold and metal NPs.

12.4.1   Role of Silver NPs in Antimicrobial Action

The presence of a Ag0 core has intuitively attributed the antimicrobial activity by most researchers. AgNPs incline to accumulate at the bacterial membrane forming aggregates when they are put in connection with bacteria and cause perforations leading to cellular death (Li et al. 2010). However, different sizes (from 1 nm to several hundreds of nm) also interact for the action mechanisms between biological components and AgNP surfaces as the particle size can propose their action mechanism slightly without a secondary species. The AgNPs generate cytotoxic action by inactivating enzymes of bacteria by producing reactive oxygen species (Kim and Ryu 2013). Some other mechanisms give a prevalent role to Ag+ species. Some systems containing initially silver (+1) species release ROS by simple dissolution or ion exchange such as salts (Valentine et al. 1998), zeolites (Sambhy et al. 2006), or ionomers (Dallas et al. 2011), which doesn't happen with metallic Ag0 nanoparticles. Thus the monovalent silver species becomes antibacterial agent keeping NPs as a reservoir. The silver ions possess affinity toward organic most notably thiols with which they form a quasi-covalent bond (Ag–S binding energy being around 65 kcal/mol), amines and phosphates. Affinity of Ag+ for selenol groups is analogous (Han et al. 2001), but these moieties are fairly uncommon in the living world. Furthermore, silver can act as a linking agent between several thiols forming aggregation of the thiol-containing molecules which are irreversible (Parikh et al. 1999). Several molecules (DNA, peptides (membrane-bound or inside the cell), or cofactors) have been recognized as the target of these ions that was observed with the dying bacteria. With contrast to the antibiotics which targets one particular constituent of the bacterial life cycle, Ag+ ions will adsorb voluntarily to any high affinity moiety; thus unlikely many pathways are affected causing the cellular death. A much more probable hypothesis would be that silver binds non-specifically to a wide variety of targets, perturbing simultaneously many aspects of the cell

metabolism and leading to its death. Among all pathways affected, some are very sensitive to little amount of silver species too. This capability to disrupt a large variety of pathways may be one reason explaining the antibacterial action of silver nanoparticles against a very broad spectrum of microorganisms. Park et al. presented that developed ROS were intricated in more than half of the antibacterial activity by comparing Ag+ action in the presence and absence of oxygenic respiration. The release of chemisorbed ions at the surface of the particles along with oxidation was another source of Ag+ ions in nanoparticulate systems (Dobias and Berrier 2013). A percentage of the novel silver salt will remain oxidized comparatively even if a mild reducing agent (such as sodium citrate) is added to the solution by remaining free in solution or bound to the surface of the Ag0 nanoparticles by a group of pending citrate ligands (Henglein 1998).

Chloride is much available in both environmental and biological systems which forms the slightly soluble precipitate AgCl. However, in presence of excess chloride, soluble silver (+1) polychloride species $AgCl_x (x-1)-$ are formed and contribute to the antibacterial activity (Chambers et al. 2013; Levard et al. 2013). The size and shape dependency of the nanoparticle also contributes to the release of Ag+ ions required to dissolve AgNPs (Pal et al. 2007); Zhang et al. 2011). The improved activity occurs due to a larger surface per unit of mass scales like $1/R$ (the number of particles scales like $1/R3$ and the surface like $R2$, with R the radius). These minor NPs reveal more active surface and are thus more prone to dissolution. For analogous reasons, accumulated NPs uncover a smaller amount of surface to the solvent than separated NPs and possess a lesser antibacterial impact (Bae et al. 2010). However, it has been recently validated by Liu et al. that the released Ag+ scale well if the samples were regularized by their exposed surface. Afterward, Xiu et al. showed in 2012 that the substantial parameters to evaluate the activity of silver nanoparticles were the silver released as Ag+ and not the quantity of primary silver added as nanoparticle (Fig. 12.1) to the solution.

The phytosynthesized AgNPs from *Urtica dioica* were explored for its antibacterial activities for a range of pathogenic microorganisms, by Jyoti et al. 2016. The inhibition zone's diameters in millimeter are presented in Fig. 12.2 and Table 12.3. The AgNPs unveiled higher activity than AgNO3 solution and leave extracts which were served as controls. Moreover, the antibacterial activities were found to be augmented with the higher concentration of AgNPs. In present study, zone of inhibition was found to be highest (27 mm) against *S. marcescens* and lowest (18 mm) against *K. pneumoniae*. These findings are in agreement with previous studies that examined antibacterial activity of AgNPs (Ghosh et al. 2012). However, the mechanism of the inhibitory action of the metal nanoparticles on microorganisms is not still clearly known and need further research assistance.
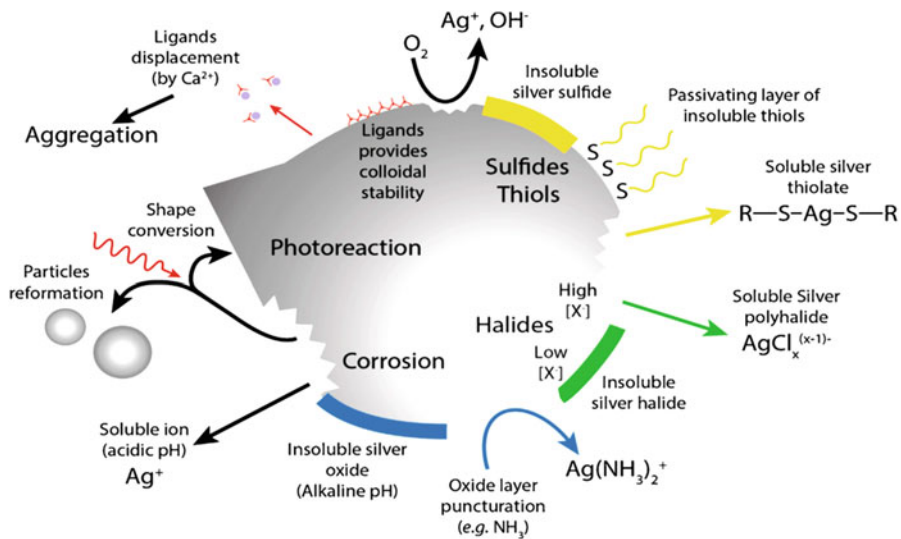
Fig. 12.1 Different methods by which silver nanoparticles react for various physiochemical, biological, and environmental conditions. (Courtesy to Nano today 2015, 10: 339–354)
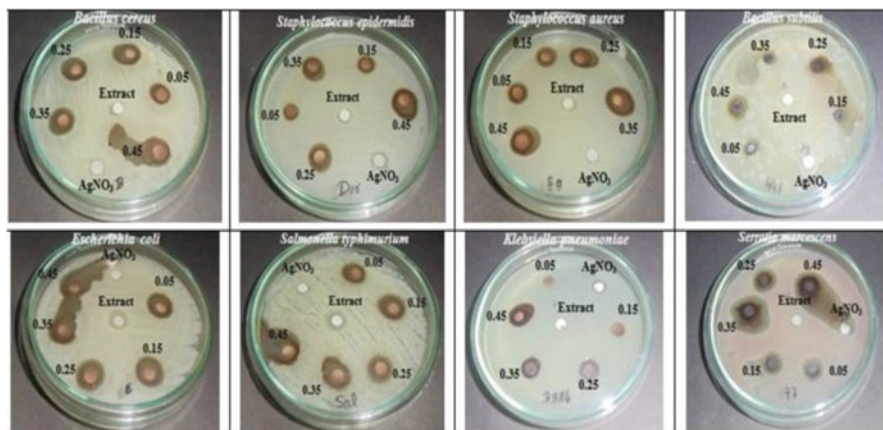
Fig. 12.2 Antibacterial activities of synthesized silver nanoparticles of *Urtica dioica*. (Courtesy to: J of Rad res and app sciences 9(2016): 217–227)

Table 12.3 Inhibition zone of AgNPs, AgNO$_3$, and *Urtica dioica Linn.* leaves extract against Gram-positive and Gram-negative bacteria

Test pathogens	Inhibition zone (mm)					Extract	Ag NO3
	0.05 mg/100 ml	0.15 mg/100 ml	0.25 mg/100 ml	0.35 mg/100 ml	0.45 mg/100 ml	0.45 mg/100 ml	0.45 mg/100 ml
B. cereus	14	15	18	23	24	–	7
S. epidermidis	9	12	14	16	19	7	8
S. aureus	12	16	17	19	21	7	7
B. subtilis	10	12	16	16	25	–	–
E. coli	12	15	16	17	19	98	–
S. typhimurium	14	17	18	19	25	–	7
K. pneumoniae	8	10	13	14	18	7	8
S. marcescens	13	15	16	24	27	–	–

Courtesy to: J of Rad res and app sciences 9(2016): 217–227

12.4.2   Applications of Gold Nanoparticles

Very recently, in the research field , many applications for gold NPs (Au NPs) starting from engineering to medicine, have been attributed (Patra et al. 2015). The biocompatibility of gold nanoparticles made them fit enough to be used in the treatment of arthritis and cancer (Jain et al. 2006) and antimicrobial therapies. Under dark-field light-scattering microscopy, Au NPs can sense endocytosis, tumor metabolites, and receptors in cells (Dykman and Khlebstov 2011). Some Au NP-based diagnostic kits are under clinical trials (Kumar et al. 2015). Green-synthesized Au NPs (Fig. 12.3) have also been used in the development of quantification of blood glucose, biosensors, toxic metals, disease markers, and insecticides (Liu and Lu 2003). Au NPs also have the potential to degrade and detoxify toxic pollutants (Lopez et al. 2004; Hernández et al. 2006). Some other applications have been shown in Fig. 12.4.

For many decades, gold has been used as a treatment in many traditional medicines. Robert Koch first explored the biocidal potential of gold (Glišić and Djuran 2014). Apart from their other applications, due to its ability for the electro-static flux across membranes, resulting in distorted membranes, the antimicrobial activity of Au NPs has been typically oppressed (Li et al. 2010). Moreover, nanoparticles also improve many gene expressions serving in redox processes leading to microbial death (Nagy et al. 2011) through smaller size, distinctive surface
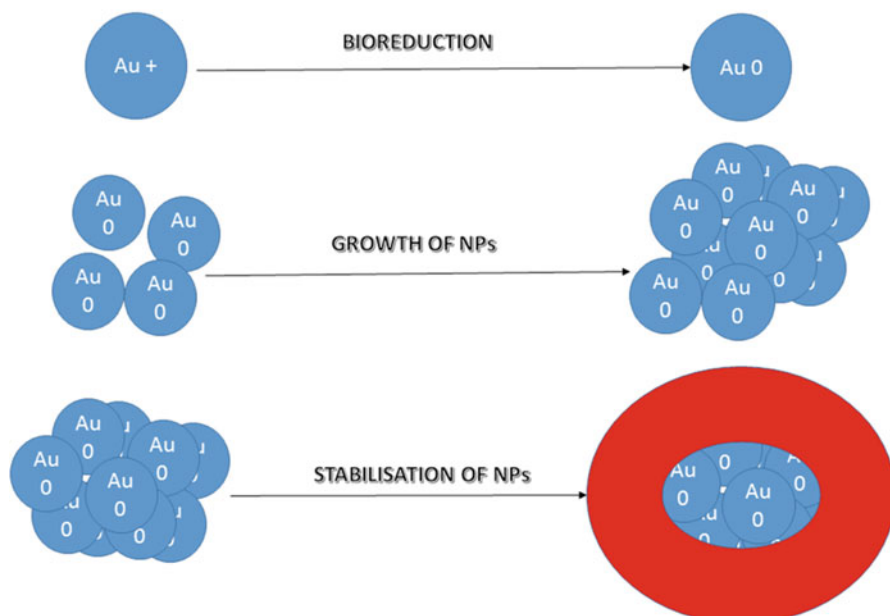
Fig. 12.3 The visual summary of gold nanoparticle synthesis and aggregation of the NPs
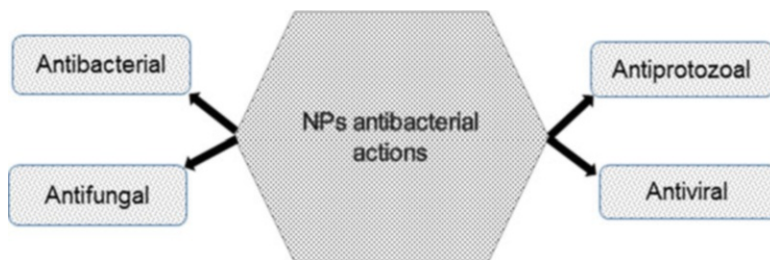
Fig. 12.4 Several antimicrobial actions of nanomaterials

chemistry, photothermic nature, and polyvalences (Gu et al. 2003; Gopinath et al. 2013). The reaction of Au Nps with sulfur- or phosphorus-holding bases leads to inactivation of enzymes (nicotinamide adenine dinucleotide (NADH) dehydrogenases), which interrupt the respiratory chains by high amount of free radical generation causing cell death. Another proposed hypothesis is that these NPs decline the ATPase activities and GNP may also prevent the tRNA binding to ribosomal subunit (Cui et al. 2012). For instance, during leishmaniasis, Au NPs produces an elevated electron numbers by yielding ROS (O − 2 and •OH). These ROS may even abolish DNA and other cellular components of the pathogen. Another possible mechanism is that these Au NPs obstruct the H+ efflux in the transmembrane.

Antimicrobial potential of the many NPs is determined by the size and surface chemistry according to Herdt et al. stating that gold surface attachment leads to DNA degradation (Brayner et al. 2006; Herdt et al. 2006). Moreover, according to Ahmad et al. 2013, a 7 nm Au NPs could confine the H+ transmembrane efflux of the *Candida* species further than the 15 nm Au NPs. Moreover, the antimicrobial activity also differs according to the cell wall composition. This was well evidenced by the Au NPs' highest activity against Gram-negative bacteria than Gram-positive bacteria due to the composition difference as described in earlier section. Other than the cell wall structure of bacteria, surface modification (coating or capping agents), concentration, and purification methods also affect the antibacterial activity (Zhang et al. 2015; Kaviya et al. 2011). The antibacterial activity efficacy of Au NPs can be enhanced by antibiotic coatings especially aminoglycoside antibiotics (Payne et al. 2016). It is very interesting that comparing green-synthesized Au NPs to chemically synthesized Au NPs shows effectual antibacterial activity against certain bacterial strains, which may be due to the synergistic effect of Au NPs and extracts (Mishra et al. 2011).

12.4.3 Metal Oxide NPs

Recently, apart from ZnO used as a wide bandgap semiconductor (3.36 eV), with potential electronic applications (Baxter and Aydil 2005) and a wide range of

nanostructures makes ZnO for nanoscale optoelectronics and piezoelectric nanogenerators (Song et al. 2006). They are used powerfully to fight microorganisms (Sawai et al. 1995). There are some reports (Sawai et al. 1995) considered which reveals by a conductometric method a considerable antibacterial activity of CaO, MgO, and ZnO, which were attributed by the generation of reactive oxygen species on the surface of these oxides. Once ZnO destroys the cell membrane, the ZnONps remain forcefully adsorbed on the dead bacteria surface preventing further antibacterial action continuing to release peroxides into the medium showing high bactericidal efficacy. From the results of another study (Stoimenov et al. 2002), it was being observed that the smaller particle size enhances the activity due to its large surface area-to-volume ratio. The thorough mechanism of ZnONP activity is still under study.

12.4.4   NP for Antifungal Action

Antifungal activity of NPs is less explored compared to antibacterial activity. Gajbhiye et al. (2009) reported efficacy of biosynthesized silver nanoparticles against *P. glomerata*, *P. herbarum*, *Trichoderma* sp., *F. semitectum*, and *C. albicans*. Moreover, they furthermore described the synergistic properties in blend with fluconazole. Jo et al. (2009) deliberated the activity of both nanoparticles and silver ions against two plant pathogenic fungi, *Magnaporthe grisea* and *Bipolaris sorokiniana*. The antifungal activity of NPs in arrangement with dissimilar heterocyclic compounds like thiazolidine, pyrazolo, phthalazine, hydrazide, tetrazolo, and pyridazine derivatives was considered against *C. albicans* and *Aspergillus flavus.* Nasrollahi et al. (2011) investigated antifungal activity of chemically synthesized AgNPs against *C. albicans* and *S. cerevisiae* explaining the potential activity of AgNPs as compared to standard antifungal agents (viz., amphotericin B and fluconazole). Pawan et al. (2012) augmented the potential antifungal activity of chitosan nanoparticles against *R. solani*, *A. flavus*, and *A. alternata* from chickpea seeds. In another study, Tile and Bholay (2012) reported significant activity of AgNPs against *Trichophyton rubrum*, *C. albicans*, and *A. fumigatus*. In an extensive study, Xu et al. (2013) evaluated AgNPs and natamycin against 216 strains of fungi demonstrating higher activity compared to natamycin. One of the possible explanations is destruction of membrane integrity of fungi and inhibition of normal budding process in yeasts (Kim et al. 2009).

12.4.5   Antiviral Activity of NPs

NPs have established marvelous care for its antibacterial activities, but the antiviral properties of metal nanoparticles continue to be an emergent area (Galdiero et al. 2011). The best known examples are West Nile virus, SARS coronavirus,

Hantavirus, monkeypox virus, Nipah virus, Chikungunya virus, Hendra virus, and, last but not least, the threat of pandemic influenza viruses, most recently of avian or swine origin (Howard and Fletcher 2012). Thus, a greater is there to develop a novel unique cure for antiviral agents, which incredulous the issue of antiviral resistance. For instance, AgNPs are developing as one of the remedies for the administration of viral diseases due to their possible antiviral activity that requires maintenance of long-lasting therapeutic regimens or circulating drug concentration. Three key aspects can be extrapolated from the studies conducted so far on the antiviral properties of NPs: (1) NPs have validated antiviral activity against many viruses affecting both prokaryotic (De-Gusseme et al. 2010; Narasimha 2012) and eukaryotic organisms, making them a true broad-spectrum antiviral agent; (2) viral inhibition even relies on the size of NPs (Speshock et al. 2010); and (3) early infection might be the general time frame where NPs exert their antiviral activity imposing the rest of the viral replication cycle (Baram-Pinto et al. 2009; Trefry and Wooley 2013). However, an exact mechanism of NP antiviral activity and a particular phase of infection at which NPs exert antiviral activity have yet to be revealed.

12.5   Limitations of the Current Research

To the surprise, it should be noted here that many antibacterial mechanisms of NPs are still uncertain. For instance, many studies point the antibacterial activity to ROS/ oxidative stress, whereas for other NPs, such as MgO NPs, the antibacterial mechanism may not be related with the regulation of metabolism of bacterial strains. Therefore, the antibacterial mechanisms of NPs are substantially relevant in addressing for future research.

The lack of cohesive standards is one limitation of the existing studies on the antibacterial mechanisms of NPs. In particular, different bacterial strains, NP characteristics, and action times were examined in different studies making it difficult to compare antibacterial activity. Thus, no solitary method accomplishes all the situations for procurement evidence about the antibacterial mechanisms of NPs as each type of NPs exhibits distinct antibacterial effects. A complete analysis is often suggested to study the probable antibacterial mechanisms.

Our other limitations are the multifaceted bacterial cell membrane structure and the deficiency of research methods for in vitro studies. Furthermore, in vitro models cannot completely sham the in vivo situation to precisely replicate the cellular body interactions. Therefore, it is intolerable to appraise the antibacterial action of NPs solely through in vitro bacterial cell culture.

Regarding nanoneurotoxicity like crossing of NPs across the bacterial cell membrane, many questions are still unanswered by the research community. The cell membrane of a bacterial is both a barrier and a channel for the movement of substances in and out. In bacterial cell membranes, especially Gram-negative strains

have porins that allow the passage of molecules of around 600 Da molecular weight across the bacterial cell body. Therefore, due to their size, almost the transport of nearly all NPs will be limited. However, certain scholars have projected that porins can facilitate the passage of NPs with thicknesses in the range of 1–9 nm through the bacterial cell membrane. Endocytosis of microorganisms, similar to what is observed for eukaryotic cells, may be measured as additional mechanism of NP movement.

In an era of increasing MDR, NPs are a feasible alternative to antibiotics and seem to have great potential to resolve the difficulty in which bacteria are evolving resistance to numerous antibiotic types, and it is becoming very hard to combat infectious diseases and treat patients, leading to serious mortality.

12.6   Antibiotic-Tagged NPs to Overcome the Current Research Limitations

As mentioned above, the researchers are facing great difficulty in designing an apt NP drug for antimicrobial therapy. Hence, they developed the idea of antibiotic-tagged NPs to reduce the MDR and its side effects. Accordingly Kumar and his coworkers in 2016 analyzed the synergistic effects of AgNPs with eight antibiotics against pathogenic bacteria (Fig. 12.5 and Table 12.4). In many cases, they could analyze that the effects of antibiotics were enhanced. Synergistic interaction of AgNPs and streptomycin showed a minute increase in the inhibition zone against seven pathogenic bacteria in the range 0.1 to 0.9 with the exception of *B. cereus* where a 6.1-fold increase was seen. When combined with kanamycin, amikacin, tetracycline, and cefetaxime, the AgNPs showed comparable synergy (a 0.1–4.4-fold increase). Amoxicillin depicted the highest overall synergistic activity as for *S. marcescens*, while vancomycin with AgNPs revealed synergistic activity against *E. coli*. A greater fold increase in case of inhibition zone was initiated against *S. epidermidis*, *B. subtilis*, and *E. coli* in the existence of a blend of cefepime and AgNPs. *S. epidermidis*, *S. marcescens*, *E. coli*, *S. typhimurium*, *Klebsiella pneumonia*, *S. marcescens*, and *B. subtilis* were found to be subdued in combination of AgNPs and antibiotics, which otherwise indicated a resistant pattern in the manifestation of the antibiotics (vancomycin, cefetaxime, ampicillin, kanamycin, amikacin, cefepime) alone. Thus it could be augmented that AgNPs enhance its efficacy in company of most of the antibiotics, against many drug-resistant bacteria (Fayaz et al. 2010; Ghosh et al. 2012; Singh et al. 2013).

Moreover, this research provides helpful insight into the development of new antibacterial agents. The combination of antibiotics and NPs will make it difficult for pathogenic bacteria to develop resistance which otherwise renders the available antibiotics inefficient; hence, this combination therapy can be further studied to develop new formulation of NPs in synergy with antibiotics.
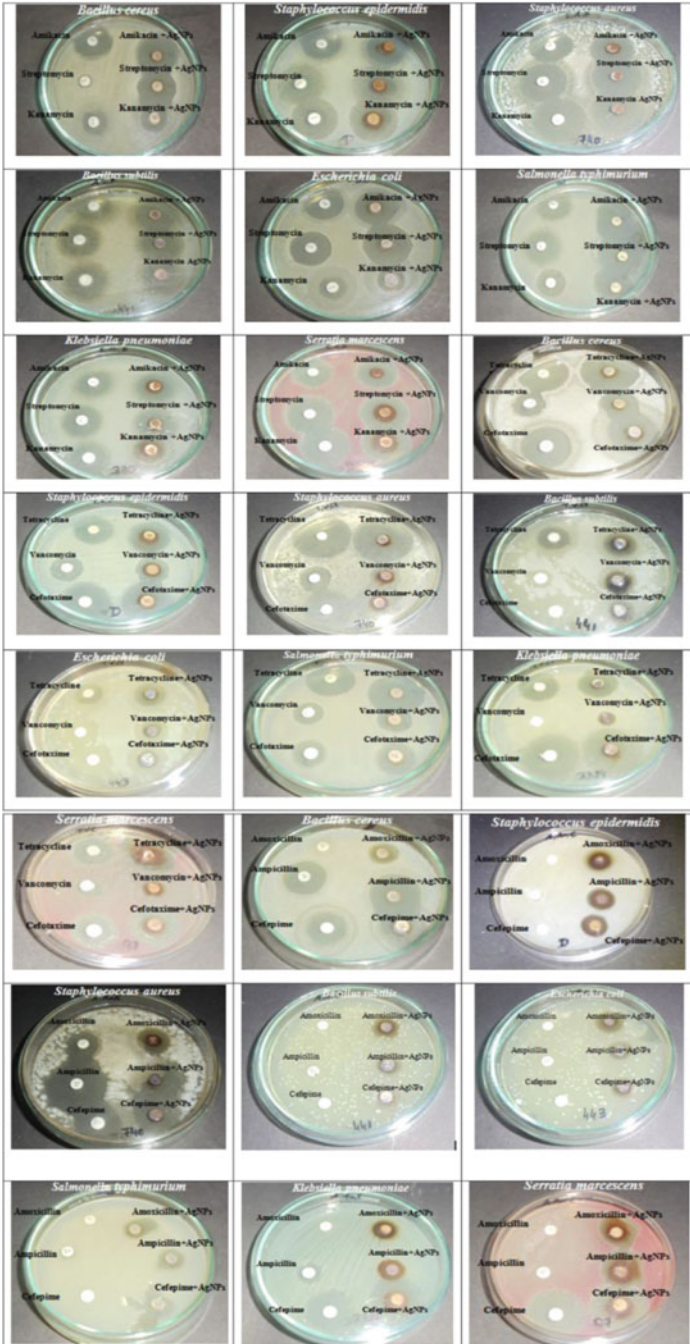
Fig. 12.5 Plates showing the increase in diameter of inhibition zone of antibiotics with AgNPs against pathogenic bacteria

Table 12.4 Inhibition zone (mm) of different antibiotics (with and without AgNPs) against Gram-positive and Gram-negative bacteria

Pathogens		Antibiotics								
		Streptomycin	Amikacin	Kanamycin	Vancomycin	Tetracycline	Ampicillin	Cefepime	Amoxicillin	Cefetaxime
B. cereus	A	09	24	15	19	21	25	22	11	33
	B	24	27	25	26	37	28	30	19	39
	C	6.1	0.3	1.7	0.9	2.1	0.2	0.8	1.9	0.4
S. epidermidis	A	27	26	25	18	22	07	06	06	25
	B	35	31	27	18	30	19	16	16	25
	C	0.7	0.4	0.2	0.0	0.8	6.4	6.1	6.1	0.0
S. aureus	A	27	29	26	13	36	29	19	15	24
	B	29	32	29	19	39	29	23	20	28
	C	0.1	0.2	0.2	1.1	0.1	0.0	0.5	0.5	0.4
B. subtilis	A	19	23	19	15	12	06	06	06	06
	B	26	26	23	21	19	13	16	13	14
	C	0.9	0.3	0.5	0.9	1.5	3.7	6.1	3.7	4.4
E. coli	A	23	22	15	06	17	06	06	06	06
	B	27	27	15	20	20	14	13	16	13
	C	0.4	0.5	0.0	10.1	0.4	4.4	3.7	6.1	3.7
S. typhimurium	A	22	24	19	12	28	06	06	06	10
	B	31	32	25	20	31	15	14	14	19
	C	0.9	0.8	0.7	1.8	0.2	5.2	4.4	4.4	2.6
K. pneumoniae	A	18	19	20	06	21	11	23	06	25
	B	21	21	22	12	25	16	28	14	30
	C	0.4	0.2	0.2	0.3	0.4	1.1	0.5	4.4	0.4
S. marcescens	A	22	26	24	11	20	06	27	06	16
	B	27	26	26	11	27	24	27	26	20
	C	0.5	0.0	0.2	0.0	0.8	15.0	0.0	17.8	0.6

Courtesy to: J of Rad res and app sciences 9(2016): 217–227

12.7 Conclusion and Future Prospects

Nanoparticles have manifold applications in numerous fields of science such as electronics, probes, disease diagnostics and treatment, remediation, imaging, and cellular transportation. Various physicochemical methods are being used to synthesize Nps. But, biogenic reduction of the salts to produce NPs is inexpensive, safe, and eco-friendly. Furthermore, NPs of desired morphology and size are also synthesized in massive amounts through this process. Their reduction potential and stability are endorsed to bioactive molecules existing in these biological resources. Among these bio-reductants, plant extracts are more advantageous than biological resources. Therefore, in this prospect, using plant sources for NPs synthesis can open new horizons in the future for antibacterial action as well.

The developing microbial resistance can be ruled out, by many means of many nanomaterials. However, several preclinical and clinical trials are on research levels for better considerations to visualize the restrictions as well as the potential of many nanoparticles to elucidate the antimicrobial mechanisms of these metallo-nanoparticles. Table 12.5 summarizes the potential applications for some nanoparticles that have received some attention in research. Unlike antibiotics that may have only one mechanism of action, nanomaterials can be related to multiple cell processes owing to its potential application in the fight against multidrug-resistant microorganisms. Once explored, it will revolutionize the microbiology world both on laboratory and commercial scale.

Representation of the studied and possible effects of ceria and conventional nanoparticles on a bacterial lipid bilayer and cytoplasm is as follows: (1) damage of the cell wall and peptidoglycan layer caused by direct contact with nanoparticles; (2) release of toxic ions; (3) damage of proton efflux bombs with serious problems on pH regulation and modification of membrane charges; (4) generation of reactive oxygen species (ROS) that can damage biological systems (degrading the cell wall); (5) reactive oxygen species (ROS) degrading DNA, RNA, and proteins that can also interfere in protein synthesis; and (6) low adenosintriphosphat (ATP) production due

Table 12.5 Some nanoparticles with their possible antimicrobial mechanism and current or future applications in health sciences

Nanomaterial	Antimicrobial mechanism	Applications
Silver (Ag)	1, 2, 3, 4, 5, 6	Potable water filters, clothing, medical devices, coatings for washing, refrigerators, food containers
ZnO	2, 4, 5	Antibacterial creams, lotions and ointment, deodorant, self-cleaning glass and ceramics
Cu/CuO	4, 5	Medical devices
TiO_2	1,4, 5	Air purifiers, water treatment systems for organic contaminant degradation, biofouling-resistant surfaces
Al_2O_3	5	Coating surfaces
CeO_2	5	Modify the material to exert antioxidant effects through altered electronic states

to acidification (mechanism 3) and reactive oxygen species (ROS) presence (mechanisms 4 and 5) (Courtesy to: Formatex 2013: 143–154).

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