Chapter 14
Recent Advancements in the Design and Synthesis of Antibacterial and Biofilm Nanoplatforms

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Contents

Abstract Bacterial infections are a major threat for the global population. Realizing the interaction between the infectious bacteria and antibacterial agents is fundamental to understand the novel therapeutic approaches that combat the bacterial infection leading to morbidity and mortality. At present situation, contemporary healthcare sectors and clinical microbiology deal with the current issue, discovering novel therapeutic strategies to overcome bacterial infections associated with rapidly accelerating multidrug-resistant bacteria. Currently, a remarkable advancement has been occurred in nanobiotechnology toward the formulation of several novel nanoparticles (NPs) that are actively participated as potential antibacterial agents. The control over morphologies and several significant features including size,

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shape, and nature of the particles made it an extensive area of research in NP synthesis. This feasibility in the technology for the development of NPs facilitates utilization of NPs in the wide range of applications including biomedicine, biosensor, and catalyst with cost-effective manner. The NP-based antibacterial agents are out grouped from the fundamental antibacterial agents such as antibiotic and antiinfective. Nanoantibacterial agents are able to address the regular complication in mechanism of antibiotic resistance including multidrug efflux pumps, permeability regulation, degradation of antibacterial agents, and untargeted site binding affinity mutations. This highly spotted nanoantimicrobial agents are developed by means of different methodologies for both research and commercial utilization. These methodologies are widely classified into physical, chemical, and biological, which are gaining significant advancements in the recent years. The present chapter critically discusses the recent development in the nanobiotechnology, availability of various methods for the synthesis of NPs, field-specific formulation of NPs, wide range of application of NPs in the healthcare sectors specifically antibacterial and biofilm, and future perspective in the field of nanobiotechnology.

Keywords Nanoparticles · Nanobiotechnology · Multidrug-resistant bacteria · Physical, chemical, and biological methods

14.1 Introduction

Antibiotic resistance is a global challenge faced by healthcare system. Scientists have labeled the emerging crisis of antibiotic resistance as dreadful. The global threat experienced by the multidrug resistance strains is mainly due to the abuse of antimicrobial agents and lack of design and development of new antimicrobial agents. The infections associated with antibiotic resistance created a considerable health and financial problem over healthcare system (Ventola 2015a). The Infectious Diseases Society of America emphasized about a faction of antibiotic-resistant microorganism such as *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp., which are named as "ESKAPE pathogens." ESKAPE pathogens are able to escape from the activity of antibiotics and represents new patterns in pathogenesis, resistance, and transmission of diseases (Pendleton et al. 2013).

The world has now reached the middle of post-antibiotic era where two million patients have infections contributed by drug-resistant bacteria only and 23,000 people die per year. The antimicrobial-resistant strain has negative impact on morbidity and mortality. The situation of antimicrobial resistance (AMR) may cause ten million deaths by 2050, which cost up to $100 trillion (Luepke et al. 2017). The main causes of death in post-antibiotic era were due to the tuberculosis, pneumonia, and gastrointestinal infections, which accounts for 30% of all deaths. The infections

caused by Gram-negative antibiotic-resistant bacteria are even difficult to treat with the conventional antimicrobials. In most healthcare settings, the early and proper identification of causative microbial agents and their antibiotic susceptibility patterns are lacking behind where antimicrobial agents are prescribed and used liberally. The resistant patterns dramatically increased when coupled with the poor disease control strategies, and this will results in the dissemination of resistant bacteria to other patients and environment (Akova 2016). The antibiotic resistance genes responsible for antibiotic resistance and associated infections are acquired by pathogenic bacteria through horizontal gene transfer (HGT). Horizontal gene transfer causes antibiotic resistance to disseminate from commercial and environmental species to pathogenic bacteria (Frieri et al. 2017). The antimicrobial resistance (AMR) is a silent pandemic, which is never expected to be cured on treatment with antimicrobials. AMR strains adapted to the adverse conditions through the evolution by escaping from the attack of antibiotics. So far, there is no single silver bullet to avoid innumerable victims of drug-resistant infections (Jasovský et al. 2016).

According to the reports, 80% of the pathogens associated with antibiotic resistance and persistent infections form biofilms (Algburi et al. 2017). Biofilms are formed by microorganisms where structured, coordinated, and functional thin layers of cell develop. The formation of biofilms is known as a survival strategy by microbes and for the establishment of infections. Host defense mechanism and antimicrobial activity are subsequently diminished against the bacteria surviving in the biofilm structure. The biofilm architecture is supported by components produced by the microorganism living inside it, and approximately 90% of the biofilm structure is made of exopolysaccharide (EPS) matrix, proteins, and DNA. The advantages of self-produced protective matrix include stable configuration to the cells, to act as a frame for the enzymes, antibiotics, and cells for attachment and mediate surface adhesion to the substrates (Vianna Santos 2014). The resistance of biofilms is related to their difficulty to penetrate the cell wall composed of EPS. This enables the unrestricted dissemination of the resistance genes among biofilm microorganism. Further, microorganisms present in the biofilms are in their stationary phase, which hinders the action of beta lactam drugs.

In addition, there is an urgent need to find and apply new antimicrobial agents or new therapeutic methods to reduce the microbial activity and combat associated infections (Algburi et al. 2017; Aziz et al. 2016). The development of resistant strains is occurring globally, which endangers the value of antibiotics. In order to escape from the antibiotic resistance crisis, enactment of necessary steps are required such as improving the tracking, diagnosis, and prescribing practices, optimizing therapeutic regimes, preventing the transmission of infections, and adopting antibiotic stewardship programs (Ventola 2015b). In this context, nanomaterials emerged as new approach for managing the microbial and biofilm infections. Several nanomaterials emerged as antimicrobial agents and drug carriers due to their unique physicochemical characteristics such as their sizes, shapes, and high surface-to-volume ratios. The ability of nanoparticles to interrupt the quorum-sensing networks present in the biofilms has been utilized as a strategy in antimicrobial therapy. Furthermore, nanoparticles have been employed as efficient

carriers of lipophilic drugs and conventional antimicrobials with improved penetration to the microorganisms and biofilms. The field of nanotechnology has gained much attention for the design and synthesis of nonconventional antimicrobials with the use of nanomaterials and nano-sized carriers. The nanomaterials are designed to combat bacterial diseases by reducing the cell viability, inhibiting the bacterial communication pathways known as quorum sensing, and eliminating resistant biofilms (Singh et al. 2017).

14.2 Emergence of Nanobiotechnology

The field of nanobiotechnology offers a wide variety of applications that range from industrial applications to biomedical applications. One of the main applications of nanoparticles is in biology and biomedical research. The advantages of use of nanoparticles in biology are the ability to engineer the nanoparticles to gain unique composition and functionalities (Wang and Wang 2014). There are several nanomaterials with different sizes, shapes, functions, and compositions with wide range of applications. These nanoparticles can be fabricated with various molecules using nanoprecipitation and lithography techniques. From ancient times, metals like copper (Cu), zinc (Zn), gold (Au), silver (Ag), and titanium (TiO_2) are well studied for therapeutic purposes due to their broad spectrum of antimicrobial activities. Recent advancements in the field of nanotechnology have recognized these metals as potential inhibitory agents for the growth of pathogenic microorganisms. In order to combat the infections by microorganisms, nanoparticles exert multiple functionalities such as inhibition/disruption of biofilms and/or enhanced intracellular accumulation of antimicrobial agents. Various nanoparticles are studied and characterized for their antimicrobial activities. Antimicrobial activity of these metal and metal oxide nanoparticles are purely dependent on their physical and chemical features. The large surface-to-volume ratio of nanoparticles ensures a broad range of reactions with the bioorganics, which is available on the surface of bacteria. The surface area will be larger with smaller nanoparticles. The increased area of nanoparticle enhances the contact with bacteria, which can augment the chemical and biological activities. The use of nanomaterials for biological application has reduced the concentration required for improved antimicrobial properties to a hundred fold (Muzammil et al. 2018).

14.3 Antibacterial and Antibiofilm Mechanism of Nanomaterials

The nanoparticles in antibacterial therapy are important as it is complementary to antibiotics. These nanoparticles are having multimodes of action. The mechanism and efficacy of nanomaterials (NMs) depends of the cell wall structure, metabolic

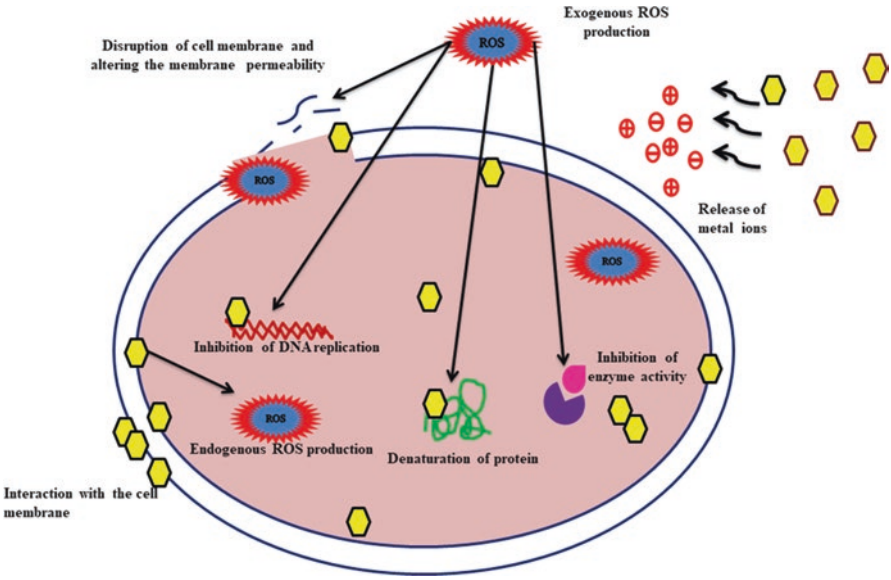

Fig. 14.1 Understanding the antimicrobial mechanisms of nanoparticles

pathways, and physiological state of bacteria and components of bacteria, which upon disruption could be lethal to the bacteria (Fig. 14.1). Other factors contributing the susceptibility of bacteria toward nanoparticles include the pH, aeration, temperature, and physicochemical properties of NMs. The major lethal pathways of NMs on bacteria are disruption of membrane integrity and cytotoxic death by production of reactive oxygen species (ROS) (Beyth et al. 2015; Aziz et al. 2014, 2015, 2019). Metal nanoparticles in contact with the bacteria can change the metabolic activity of bacteria. The ability of NMs to enter the biofilms and eliminate the bacteria represents an enormous advantage for curing the diseases. The nanomaterials in contact with bacteria form electrostatic attractions, vander Waals forces, hydrophobic interaction, and receptor-ligand interactions. A nanomaterial once gains the access to the bacteria, crosses the cell membrane, and interferes with the metabolic activity. This will influence and alter the shape and function of cell membrane. Further, these NMs on interaction with the bacterial biomolecules such as DNA, protein, ribosomes, enzymes, and lysosomes lead to the changes in cell membrane integrity and permeability, heterogeneous alterations, enzyme inhibition, protein deactivation, altering gene expression, electrolyte balance disorders, and oxidative stress. All these mechanism can be widely categorized as oxidative stress, non-oxidative mechanism, and metal ion release (Wang et al. 2017). Metal oxide nanoparticles such as silver and zinc exhibit antibacterial mechanism through free metal ion toxicity, which arises from the release of metal ions from the surface of metal nanoparticles (Dizaj et al. 2014).

14.4 The Antibiofilm Mechanisms of Materials

The antibacterial and antibiofilm mechanism of nanomaterials depends on size, shape, surface area, charge, and competence of nanoparticles. Metal- and metal oxide-based nanoparticles are widely studied for their antimicrobial and antibiofilm properties. These nanoparticles exhibit microbicidal properties by the production of ROS, which disrupts physical structures, metabolic pathways, and synthesis of DNA, ultimately leading to cell death (Fig. 14.2). Nanoparticles are fabricated in different methods for different antimicrobial and antibiofilm applications. The fabrication techniques are categorized as top-down or bottom-up methods (Gold et al. 2018). The top-down approach is initiated with the bulk material to nanoscale products through attrition or ball milling. This method results in the production of nanocomposites with broad size distribution, increased impurities, and nonuniform particle geometries. The bottom-up approach exploits varied methods to synthesis nanoparticles from raw materials and environment for the production of particles with consistent shape, size, and geometry. Such fabrication techniques include sol-gel nanofabrication, atomic layer deposition, and colloidal methods (Biswas et al. 2012).

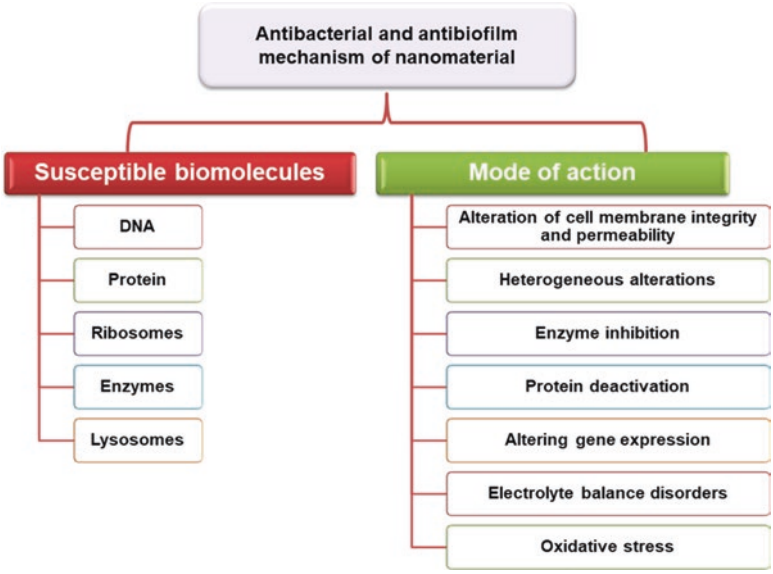

Fig. 14.2 Mode of actions and susceptible biomolecule in nanoparticles mediate antimicrobial and antibiofilm activities

14.5 Physical Properties of Nanoparticles Favoring the Antimicrobial Mechanisms

The antibacterial and antibiofilm mechanism of nanoparticles are not purely dependent on the material chemistry but also on their physical properties including the shape, size, solubility, agglomeration, and surface charge of nanoparticles.

14.5.1 Size

The nanoparticles with smaller size are able to penetrate the bacterial cell walls exhibiting higher antibacterial effect. Nanoparticles with smaller than 30 nm are effective antibacterial agents due to their higher surface-to-volume ratio. In a study, spherical nanoparticle with a diameter of 5 nm showed higher reactivity to the cell membrane of *E. coli* (Morones et al. 2005). The antimicrobial mechanism of nanoparticles is size dependent, which varies greatly from that of particles with larger diameter and also from their bulk counter parts. The nanoparticles with potential antibacterial mechanism and desired particle size are synthesized by controlling the synthesis parameters such as solvent polarity, concentration of substrates, density, and stabilizing agents (Jadhav et al. 2011). Platinum nanoparticles with 1–3 nm size showed bactericidal effect against *P. aeruginosa*, whereas those with 4–21 nm showed bacterial compatible properties (Gopal et al. 2013). Silver nanoparticles with an average size of 13.15 nm diameter proved to have better antibacterial and antibiofilm properties against imipenem-resistant *P. aeruginosa* than the bulk silver (Ali et al. 2018). Zinc oxide nanoparticles presented reduced viability and toxicity against *E. coli* and *S. aureus* when exposed to decreasing size of nanoparticles (Jiang et al. 2009). Authors examined the antibacterial activity of silver nanoparticles synthesized with different shapes and sizes. Better antibacterial activity was demonstrated by spherical-shaped smallest silver nanoparticles of 15–50 nm diameters against *P. aeruginosa* and *E. coli* (Raza et al. 2016). Nanosilver with 100 nm size did not show any bactericidal effect on methicillin-resistant *S. aureus* (MRSA), whereas 10 nm particles effectively inhibited MRSA (Ayala-Núñez et al. 2009). It was confirmed in another study that silver nanoparticles synthesized with two different sizes (10 and 100 nm) displayed different antimicrobial effect against *Methylobacterium* spp. The more antibacterial activity of 10 nm-sized nanoparticles was correlated with the larger surface area of silver nanoparticles. Particles with more surface area can possibly release more ions, which act as a vital factor in the antibacterial mechanism (Jeong et al. 2014).

14.5.2 Shape

Morphology or shapes of nanoparticles are correlated with the bactericidal activities exerted by nanoparticles. Raza et al. (2016) studied the varying antiseptic effect of spherical and triangular nanoparticles against *P. aeruginosa* and *E. coli* (Raza et al. 2016). The antibacterial and antibiofilm activity of nanoparticle changes according to their nature and shape. In a study, silver nanoparticles found to be a strong bactericidal agents when in truncated triangular shapes than in spherical or rod shape (Pal et al. 2007). Yttrium nanoparticles (Y_2O_3) synthesized in prismatic shape showed greater antibacterial activity against *P. desmolyticum* and *S. aureus*. This is probably due to the interaction of prismatic Y_2O_3 with the bacterial cell membrane, which leads to the breakage of membrane (Prasannakumar et al. 2015).

14.5.3 Zeta Potential

Increased bactericidal activity exerted by nanoparticles can also be contributed by their electronic effects or zeta potential. This can be well explained by the strong electrostatic interactions formed between the nanoparticles and negatively charged bacterial membrane. This attracts the bacteria to adhere or attach to the nanoparticles and finally permits the entry of these materials into the bacteria. The strong zeta potentials developed between bacterial membrane and nanoparticles cause membrane penetration, disruption of membrane, bacterial flocculation, and finally reduction of cell viability (Wang et al. 2017). Mostly, nanoparticles imparted with positive charge are involved in the development of strong electrostatic attraction with the bacterial cell membrane. In addition to the positively charged nanoparticles, negatively charged particles also involved in the antibacterial activity due to their molecular crowding, eventually leading to the interaction between nanoparticle and bacterial membrane (Arakha et al. 2015). Silica nanoparticles grafted with charged cobaltocenium was conjugated with penicillin for higher antibacterial activity against *P. aeruginosa*, *K. pneumonia*, *E. coli*, and *P. vulgaris.* Nanoconjugates with cationic charges and antibiotic exhibited synergistic activity leading to the enhanced lysis of bacteria when compared to the individual polymers (Pageni et al. 2018). Surface functionalization or modification imparts desired charges or electronic states to nanoparticles. Generally, polycationic chitosan can attach to the surface of bacteria, which leads to the decreased osmotic stability of cell and finally leakage of intracellular components. Authors discussed enhanced antimicrobial effect of chitosan silver nanoparticles than the free chitosan and silver. Chitosan was able to attract the bacteria due to their positive charge, and smaller-sized silver nanoparticles induced pores on cell membrane and hence together caused fragmentation of bacteria (Banerjee et al. 2010). Magnesium oxide synthesized through aerogel procedure showed enhanced bactericidal effect against *Bacillus megaterium*, spores of *Bacillus subtilis*, and *E. coli* due to the positive charge they possess (Koper et al. 2002).

14.5.4 Agglomeration and Doping Modification

The extensive use of nanoparticles in clinical trials is limited by their agglomeration effects. Agglomeration of nanoparticles has reduced their wide application in biology and medicine. Agglomerated nanoparticles showed lesser antibacterial effect than free particles (He et al. 2014). Solubility and agglomeration of nanoparticles play important role in the cytotoxicity and genotoxicity. Agglomeration of nanoparticles can be prevented by doping modification of nanoparticles. Solubility of nanoparticle influences the agglomeration effects of particles, and this controls the interaction of nanoparticle with the bacterial system. Agglomerated nanoparticles limit the ability to enter the cell and production of cytotoxic species. This is attributed by the general decrease in the surface area exposed to the bacterial system. In contrast, when nanoparticles are not agglomerated, they are able to penetrate the bacteria and produce reactive oxygen species, which are lethal to bacteria. The interactions of nanoparticles in their dispersed medium, pH, and surface charge also contribute to their agglomeration (He et al. 2014; Ahamed et al. 2008). The antibacterial activity of zinc oxide nanoparticles is altered when doped with fluorine. Zinc nanoparticles doped with fluorine produced more ROS and exhibited greater antibacterial effect than undoped nanoparticles (He et al. 2014).

14.6 Synthesis of Nanoparticles

There are numerous methods employed for the synthesis of different types of nanoparticles (Fig. 14.3). In general, all the methods are categorized into three different, physical, chemical, and biological methods. Physical methods apply usually high temperatures for the synthesis. The demerits of physical synthesis include the time required for synthesis, space, and detrimental environmental effects. The advantages of this method are the absence of solvent contamination and uniformity in the distribution of nanoparticles when compared to the chemical method of synthesis. The concentration and size of the nanoparticles vary with the temperature employed for the synthesis. Nanoparticles in solution are synthesized using laser ablation method of bulk metals (Abou El-Nour et al. 2010).

Chemical synthesis is widely used for the synthesis of metal nanoparticles. Chemical synthesis method includes three main components, namely, the metal precursor, reducing agent, and stabilizing/capping agent. In the chemical reduction method, reduction is attained by employing different organic and inorganic reducing agents. Chemical methods include the nucleation of metal ions and then formation of metallic colloidal nanoparticles by agglomeration into oligomeric clusters. Chemical synthesis of nanoparticles yields more nanoparticles than physical methods. Other type of chemical synthesis includes electrochemical synthesis, UV initiated photo reduction, photoinduced reduction, and microemulsion method (Zewde et al. 2016).

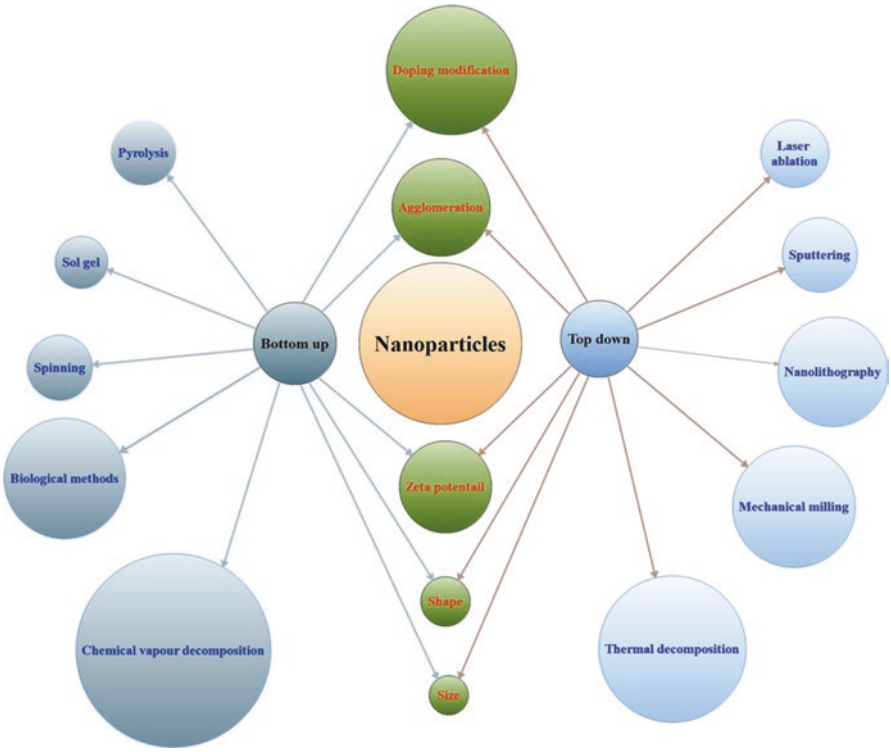

Fig. 14.3 Design and synthesis of nanoparticles through different synthesis routes

Biological method of nanoparticle synthesis also known as green synthesis is the most feasible method over physical and chemical method. Biological synthesis couples the reducing ability of microbial cells, biological molecules, and enzymes (Prasad et al. 2016). Green synthesis of nanotechnology integrates biological entities such as plants, bacteria, and fungi due to their capability to reduce metals to nanoparticles (Prasad et al. 2018a, b). Biological synthesis involves environmental friendly process and is advantageous over physical and chemical methods. Another merit of biological synthesis part is the production of the highly stable nanoparticle compared to other methods (Fernando et al. 2018). Plants are rich source for phytochemicals and enzymes. These phytochemicals are able to reduce various metal ions in to nanoscale materials. Greener synthesis offers a cost-effective renewable source for the large-scale synthesis of nanoparticles (Ahmed et al. 2016; Prasad 2014). Phytochemicals present in green tea leaf and black tea leaf such as polyphenols, flavonoids, and phenolic compounds were studied for the reduction of silver ions to silver nanoparticles and for their stabilization (Nishibuchi et al. 2012). Some of the bacteria like *Lactobacillus* sp., *Klebsiella pneumonia*, *Enterobacter cloacae*, *E. coli*, *Acinetobacter* sp., *P. aeruginosa*, and *S. aureus* are known for the synthesis

of silver nanoparticles (Fernando et al. 2018). Fungi like *Fusarium* sp. produce nitrate reductase enzyme and some capping agents, which reduce silver ions and are responsible for the long-term stability of nanoparticles (Ingle et al. 2008; Prasad et al. 2016).

Altogether, physical, biological, and chemical synthesis routes are coming under either of two broad methods known as the bottom-up and top-down methods. Bottom-up methods include different synthesis routes such as biological synthesis, pyrolysis, spinning, sol-gel, and chemical vapor deposition methods. Laser ablation, sputtering, thermal decomposition, mechanical milling, and nanolithography are the some common top-down or destructive methods of nanoparticle synthesis (Anu Mary Ealia and Saravanakumar 2017).

14.7 Different Methods of Synthesis of Nanoparticles

14.7.1 Physical

Physical synthesis of nanoparticles involves the synthesis in the absence of a solvent, which allows the uniform size distribution of nanoparticles compared to the chemical methods. Some of the important physical routes are laser ablation, evaporation-condensation, thermal decomposition**,** arc discharge method, and ultrasonic spray pyrolysis (De Matteis et al. 2018). Among all physical routes, laser ablation is unique and important method, which synthesizes pure and metallic nanoparticles without the use of chemical reagents. Even though hazardous chemicals are not utilized in physical methods, limitations of large energy consumption and longer times to get thermal stability for nanoparticles make physical routes as unfeasible in synthesis (Zhang et al. 2016).

14.7.2 Chemical

Chemical reduction, microemulsion techniques, sonochemical method, sol-gel, and microwave-assisted synthesis are the common chemical synthesis methods. Chemical methods open up the possibility of obtaining monodispersed nanoparticles having tunable size with low cost and rapidity of steps in synthesis. However, the toxic elements and hazardous chemicals employed create the difficulty in purification of particles. Even though physical and chemical routes are proven to be appropriate for the synthesis of large-scale nanoparticles, recent developments made efforts to create eco-friendly approach through the greener synthesis of nanoparticles (De Matteis et al. 2018).

14.7.3 Biological

The emergence of eco-friendly methods in the area of material synthesis has acquired much attention and expanded more into biological applications. Diverse groups of inorganic nanoparticles with distinct chemical composition, shape, size, and morphology have been designed using different microorganisms and plants for their wide variety of applications in antimicrobial therapy (Li et al. 2011). Nanoparticles produced through biogenic process are always superior in characteristics than those by chemical routes. Despite the fact that chemical routes are always able to produce nanoparticles in large scale in short time, they are costly methods and harmful to the environment and human health. The biogenic enzymatic process for nanoparticles is supported by several microorganisms that thrive in ambient conditions of varying pH, pressure, and temperature. These nanoparticles produced through biological methods are having greater specific surface area and higher catalytic reactivity (Bhattacharya and Mukherjee 2008). The nanoparticle synthesis through microorganisms can be classified as intracellular and extracellular according to the cellular site where particles are synthesized. Usually, microorganisms grab the target metal ions from their surroundings and then convert them into respective nanoparticles through the action of enzymes produced by their metabolic activities (Li et al. 2011; Prasad et al. 2016).

14.8 Antimicrobial Applications of Nanoparticles

Metal and metal oxide nanoparticles are widely explored and studied for their great potentials as antimicrobials and antibiofilm agents. The antimicrobial effect exhibited by these nanoparticles is measured as the function of their surface area in contact with the microbial cells. The small size and high surface-to-volume ratio of nanoparticles augment the interaction between them and cell membrane of bacteria to perform wide range of antimicrobial applications (Table 14.1). The antimicrobial applications of nanoparticles range from water treatment plants to synthetic textiles, to biomedicine, to surgical devices, to food processing and packaging when nanoparticles are embedded on to the surfaces (Khan et al. 2017).

Silver nanoparticles are known as strong antibacterial and antifungal agents. It has shown strong cytotoxicity against wide variety of microorganism. Rai et al. (2009) studied the antibacterial activity of silver nanoparticles against *E. coli*, *P. aeruginosa*, and *S. aureus*. The antibacterial activity of silver nanoparticles was size dependent and showed cytotoxicity in the range of 1–10 nm size, which attach to the surface of bacterial cell. This interrupts the common cell membrane function like respiration and changes the membrane permeability. In a study, silver nanoparticles showed antifungal activity against two plant disease causing fungi, *Magnaporthe grisea* and *Bipolaris sorokiniana*. In vitro experiments revealed that silver nanoparticles inhibited the colony formation of these pathogenic fungi (Jo

Table 14.1 Antimicrobial mechanism and applications of nanoparticles synthesized through different methods

Nanoparticles	Antimicrobial mechanisms	Method of synthesis	Physiochemical characteristics of nanoparticles	Test microorganism	References
Silver	Inhibition of DNA replication, expression of ribosomal proteins, and bacterial electron transport chain	Green synthesis using leaves and fruits of *Calotropis procera*	90–100 nm	*Vibrio cholerae* and enterotoxic *E. coli* (ETEC)	Reidl et al. (2014)
	Interaction of silver ions with the bacterial cell wall, alter the membrane integrity by decaying lipopolysaccharide molecules, and form pits	Modified Tollens' method in conjunction with phytochemicals	Spherical shape, 45 nm	*E. coli and S. aureus*	Grinham et al. (2019)
Zinc	Inhibition of adenylyl cyclase activity and reduction in the levels of this second messenger	Green synthesis using leaves and fruits of *Calotropis procera*	90–100 nm	*Vibrio cholerae* and enterotoxic *E. coli* (ETEC)	Reidl et al. (2014)
	Damage to the cell wall due to the localized interaction of ZnO with the membrane, improved membrane permeability, uptake of NPs due to loss of proton motive force and uptake of toxic released zinc ions	Microwave decomposition, simple wet chemical route, hydrothermal synthesis, solvothermal method, deposition process, and simple precipitation method	2 μm, 8–10 nm, 12 nm, 45 nm, and 80 nm	*S. enterica serovar* Enteritidis, *P. aeruginosa*, *S. aureus*, *E. coli*, *C. jejuni*, and *E. coli O157:H7*	Seeni et al. (2015)
Gold	Alteration of cell membrane potential and reduced adenosine triphosphate (ATP) synthase activities, which results in the reduced metabolic activities. Interruption of tRNA binding to the ribosomal and disintegrating its biological function	Chemical synthesis using sodium borohydride as a reducing agent	6–40 nm	Enteric human pathogens; *E. coli*, *S. aureus*, *B. subtilis*, and *K. pneumonia*	Shamaila et al. (2016)
	Size-dependent mechanism	Green synthesis using leaves of *Pergularia daemia*	Spherical shape, 10 nm	*S. aurous*, *P. aeruginosa*, and *E. coli*	Rajendran (2017)
Titanium oxide	Interaction with the cell membrane, reactive oxygen species generation, and photooxidation of intracellular components causing cell death	Sol-gel method	Anatase type, 13 nm	*E. coli*, *P. aeruginosa*, *K. pneumoniae*, and *S. aureus*	Desai and Kowshik (2009)
	Antibacterial, antibiofilm mechanisms, and photooxidation		Less than 50 nm	Methicillin-resistant *S. aureus*	Jesline et al. (2015)

(continued)

Table 14.1 (continued)

Nanoparticles	Antimicrobial mechanisms	Method of synthesis	Physiochemical characteristics of nanoparticles	Test microorganism	References
Copper oxide	DNA degradation, reduction of bacterial respiration, alteration in the conformation, and electron transference of cytochrome reductases	Synthesis using soybean extract	Quasi-spherical shape, 5.67 nm	*E. faecalis*, *E. coli*, and *S. aureus*	Morales-Sánchez et al. (2017)
	Release of copper ions, penetration in to the cell membrane, and disruption of cell membrane. Disruption of biochemical pathway by chelating with the enzymes and DNA damage	Synthesis using sodium borohydride in the presence of ascorbic acid as antioxidant	Spherical shape, 5.3 nm	*E. coli*, *S. aureus*, and *C. albicans*	Bogdanović et al. (2014)

et al. 2009). Silver nanoparticles are known for their antiviral activities and exhibited antiviral activity against human immunodeficiency virus type 1 in their noncytotoxic concentrations (Ahmed et al. 2016).

Nanoparticles synthesized through green approach using aqueous extract of *Acorus calamus* rhizome inhibited the growth of phytopathogens affecting the yield of vegetable crops. In the above study, *P. aeruginosa* was more susceptible to iron oxide nanoparticles than manganese oxide nanoparticles. Iron oxide nanoparticles showed complete growth inhibition of *Aspergillus flavus* (Arasu et al. 2019). Magnesium oxide nanoparticles synthesized in an average size of 68.02 nm using the brown algae *Sargassum wightii* revealed broad spectrum of antibacterial and antifungal activities against human pathogens such as *S. aureus*, *E. coli*, *P. aeruginosa*, *S. typhimurium*, *S. marcescens*, *P. mirabilis*, *A. niger*, *N. oryzae*, *F. solani*, and *Chaetomium* sp. (Pugazhendhi et al. 2019).

Novel nanoconjugates were prepared using chitosan-polyvinyl chloride polymers comprising silver nanoparticles and exhibited excellent antibacterial activity against *S. aureus*, *E. coli*, *P. aeruginosa*, *S. typhimurium*, and *L. monocytogenes* after 30, 60, and 120 min of exposure (Gaballah et al. 2019). Biomaterial immobilized with subtilisin conjugated gold core and silver shell nanoparticles exhibited excellent antibiofilm potential against *S. aureus* and *E. coli* than the free silver-gold nanoparticles (Prabhawathi et al. 2019). Another biomaterial immobilized with silver and titanium dioxide nanoparticles was found to be excellent antibacterial agents for long-term applications. Biomaterial was prepared by incorporating the silver and titanium nanoparticles into cellulose acetate nanofibers. The nanocomposite nanofibers showed antibacterial activity against *E. coli* and *S. aureus* for 36 h, and the bacterial growth was inhibited up to 72 h (Jatoi et al. 2019). Metal fluoride nanoparticles were used as antibacterial and antibiofilm agents due to their low solubility and provided prolonged protection from pathogens. Yttrium fluoride nanoparticle-coated catheters were able to inhibit the bacterial colonization and finally biofilm formation by two common nosocomial pathogens such as *E. coli* and *S. aureus* compared to the uncoated catheters (Lellouche et al. 2012). Multifunctional nanoparticles were prepared containing amphiphilic silane and photosensitizers like coumarin 6 and chlorine 6 for investigating antimicrobial photodynamic therapy against periodontitis pathogens. Multifunctional nanoparticles reduced the biofilms of *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Streptococcus sanguinis* than the control groups. The CFU was reduced by 4–5 orders of magnitude after the photodynamic therapy of pathogens (Sun et al. 2019). Hybrid nanomaterials synthesized using two different antibacterial agents like graphene oxide and biogenic silver nanoparticles were used as anti-adhesion agent, which prevented the biofilm formation to 100% after 1 h of exposure to the nanomaterials (de Faria et al. 2014). Khalid et al. (2019) has synthesized silver and iron oxide nanoparticles coated with rhamnolipids having antibacterial, anti-adhesive, and antibiofilm properties. Biosurfactant coated nanoparticles showed synergistic antibacterial and anti-adhesive properties against biofilms of *P. aeruginosa* and *S. aureus* due to the production of reactive oxygen species by rhamnolipids (Khalid et al. 2019).

The antibacterial and antifungal efficacy of nitric oxide was enhanced by employing silica nanoparticles releasing nitric oxide. The nitric oxide-releasing silica nanoparticles inhibited the growth of biofilms formed by *E. coli*, *P. aeruginosa*, *S. aureus*, *S. epidermidis*, and *C. albicans* by 99% (Hetrick et al. 2009). Antimicrobial peptide conjugated with metallic nanoparticles gained much interest in the field of medicine, due to their increased solubility of peptide molecules and potential enhanced antimicrobial activity especially toward broad range of drug-resistant bacteria. Vancomycin-conjugated gold nanoparticles showed enhanced antimicrobial activity against vancomycin-resistant *S. aureus* (VRSA) (Rajchakit and Sarojini 2017). There are several groups of nanoparticles and their nanoconjugates, which are in high demand to replace the inefficient antibiotics for eliminating antibiotic-resistant microorganisms and their biofilms.

14.9 Future Prospects and Summary

Nanotechnology has become one of the promising alternatives applied in broad areas of science. The term nanobiotechnology attained much attention in the scientific filed due to their wide spread applications biomedical field. The potential use of nanoparticles for the treatment of microbial infections caused by drug-resistant microbial cells and their biofilms is accelerating in the modern research. More recent progression in the development of nanoparticles has enhanced the applications of nanosized products in healthcare products such as drug delivery scaffolds, burn dressings, water purification systems, and antimicrobial agents. Since the commencement of nanoparticle synthesis over the centuries ago, researchers were in the pursuit of exploiting novel methods of nanoparticle production in an optimized manner for various applications. The physicochemical characteristics of nanoparticles are having much significance on their function, and extensive studies are required to explore and fully understand the synthesis of these particles. Different kinds of physical, chemical, and biological methods are available to engineer, modulate, and fabricate ideal size, shape, and other morphology of nanoparticles for antimicrobial applications. The application of green chemistry in nanoparticle synthesis has revolutionized the field of nanobiotechnology. The green synthesis is a cost-effective and eco-friendly method for the large-scale synthesis of nanoparticles. Various methods of nanoparticle synthesis and their applications as antimicrobial and antibiofilm agents are explained in this chapter. The strong inhibitory and microbicidal activities of nanoparticles toward bacteria, fungi, and viruses and their mechanism of action was discussed with along with their antibiofilm mechanisms. Furthermore, there are many biogenic methods and other routes still not explored for the production of nanoscale products. Novel synthesis routes need to be figured out in the future with the goal of scalable production and fabrication of nanoparticles for their successful application in antimicrobial therapy.

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