Chapter 1
Nanomaterials: Therapeutic Agent for Antimicrobial Therapy

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R. Prasad et al. (eds.), *Nanostructures for Antimicrobial and Antibiofilm Applications*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-40337-9_1

Abstract In recent time, nanomaterials have been developed as the most auspicious therapeutic remedy toward the infectious microbes, which cannot be healed through traditional treatments. The ancient age treatments via antibiotic drugs are now failed toward microbes, owing to their heavy and unnecessary high dose consumption by the common people. Now, the microbes have become resistant to these antibiotic medicines, and therefore, the nanomaterials came in light to tackle these rising problems related to microbe infections.

Among the various nanomaterials, the carbonaceous nanomaterials (including carbon nanotubes, fullerene, graphene oxide, reduced graphene oxide) and heavy metals (gold, silver) and their oxides (silver oxide, titanium dioxide, zinc oxide, copper oxide) are more commonly employed as antimicrobial agent. In this chapter, we have discussed the antimicrobial activity of these nanomaterials and their mode of action/mechanism. Their unique small size, high surface/volume ratio, large inner volume, and unique chemical and physical properties resulted in efficient antimicrobial activity or antibiofilm activity. Generally, antimicrobial activity/property of the nanomaterials is mainly dependent on the composition, surface modification, and intrinsic properties of the nanomaterials as well as type of microorganism. In this book chapter, the future aspect and challenges faced by nanomaterials toward efficient and effective bactericidal effect are also discussed.

Keywords Nanomaterials · Metal and metal oxides · Carbonaceous materials · Bacterial cell

1.1 Introduction

Nowadays, bacterial infection and their adhesion and rapid growth have become a serious concern for everyone, either they are common person or industry peoples associated with textile, food packing, water treatment, and marine transport-based industries (Diez-Pascual 2018). In recent years, due to the antibiotic resistant behavior of bacterial cells, their infections and related problems have been hiked enormously. According to the World Health Organization (WHO), approximately 25,000 deaths have been occurring by bacteria per year in Europe (Cambau et al. 2018). Researchers and scientists are working very hard to find an effective and helpful solution for not only killing the bacterial cells but restrict their growth in very initial phase also.

In general, an antimicrobial agent is substance/compound/material, which can either kill or prevent the growth of microorganism like fungi, bacteria, protozoans, and other microorganisms. In the nineteenth century, two microbiologists Louis Pasteur and Jules Francois Joubert had their first observation of microorganisms and first discovered one type of bacteria that can prevent the growth of another type of bacteria. From that time till date, several antimicrobial agents have been discovered

to prevent or kill the microorganisms' growth. Mainly model antimicrobial agents must have the following criteria to work effectively against microorganisms:

1. The model antimicrobial agents should have capacity to selectively inhibit the growth of microorganism.
2. Destroy the targeted organism while keeping other organisms safe and intact.
3. Their solubility as well as stability should be higher in body fluids.
4. Model antimicrobial agents must have easy and cost-effective availability in the market.
5. They should have high activity for longer period of time.

The most commonly used antibacterial agents can be either pure natural products like aminoglycosides or chemically modified natural compounds (like penicillins, cephalosporins etc.) or pure synthetic antibiotics like sulfonamides also (Hajipour et al. 2012). In general, the antibacterial agents can be classified in two classes: (1) bactericidal and (2) bacteriostatic. Bactericidal agents are class of compounds used to kill the bacterial cell, while bacteriostatic agents retard the growth of bacteria. Antibacterial agents, in the form of antibiotic, are usually provided to fight against the infectious diseases and kill the bacterial cells, but due to their high-dose use and frequent intake, now, bacterial cells have created a resistant for the ancient antibiotic drugs. Now, the antibiotics or antibacterial agents failed to kill the bacterial cell, and this has become the major problem all over the world.

Therefore, newer, essential, and effective antibacterial agents are required to be developed to overcome the problem of antibacterial resistance. We need new, cost-effective antibacterial agents which should be highly effective toward bacteria but exhibit almost negligible side effects. In the last few decades, nanomaterials have been well researched, developed, and used in several fields, and therefore researchers hope that they will solve this problem also. Therefore, nanomaterials like gold, silver, zinc oxide, and carbonaceous materials are nowadays very popularly synthesized and used as antibacterial agents. Now comes the very important question why nanomaterials have improved properties as antibacterial agent. The most common answer to this question would be the large surface to volume ratio of nanomaterials, which results in their various outstanding properties and features. In this chapter, we have focused on the use of nanomaterials as an effective antibacterial agent and also discussed the true reasons for their high success rate.

1.1.1 Basic Discussion About Bacterial Cells

Before discussing about the role of nanomaterial as antibacterial agent, let's discuss some basic things about the bacterial cells and their structure. The bacteria cell wall is prepared in such way that it can protect themselves from mechanical stress and osmotic rupture. Two types of bacteria cell wall are commonly studied, i.e., Gram-positive and Gram-negative cell wall. In the Gram-positive bacterial cell, a thin layer (20–50 nm) of peptidoglycan is present at the outer surface along with teichoic

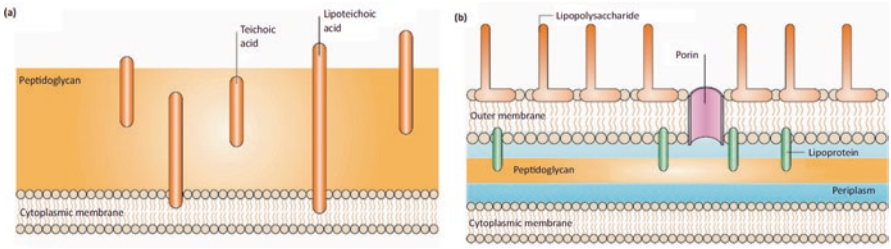

Fig.1.1 Cell wall structures of Gram positive (**a**) and Gram negative (**b**) bacteria (Reproduced with permission from Hajipour et al. 2012)

acid. Structure of Gram-positive bacteria cell is not very complex, but structure of Gram-negative bacteria cell wall is quite complex. Gram-negative bacteria contain outer membrane and peptidoglycan layer, which is connected by the lipoproteins. The outer membrane of Gram-negative bacteria plays crucial role to protect them from any kind of external effect and impact (Hajipour et al. 2012). The cell wall of the bacteria plays important function to efficiently resist from antimicrobial agents. The cell wall structures of Gram-positive and Gram-negative bacteria are shown in Fig. 1.1 (Hajipour et al. 2012).

1.1.2 How Nanomaterials or Antibacterial Agent Interact with Bacteria: Probable Mechanism

The exact mechanism of nanomaterial action toward the bacterial cells is still on debate. However, various literatures have been reported where some of mechanisms have been proposed and discussed (Fernando et al. 2018; Aziz et al. 2014, 2015, 2016). According to the literature, some of the common mechanisms are given below (Deus et al. 2013):

1. Nanomaterials that interact with cell membrane bind directly or indirectly through it and finally kill the cell.
2. Release of metal ions/compounds from the nanomaterials that can bind the sulfur containing proteins of the cell membrane inhibit the cell penetrability and destroy the cell membrane.
3. Generation of reactive oxygen species (ROS) can destroy the cell membrane.
4. Protein oxidation, obstacle the electron transport, and membrane potential breakdown because of nanomaterials contact with the cell membrane.

The probable mechanism discussed above does not operate individually, more than one mechanism are operated at a time. In the next section, we have discussed the details of these mechanisms.

1.1.2.1 Interaction of Nanomaterials with Bacterial Cell Membrane

It has been found that nanomaterials or antibacterial agents firstly interact with the bacterial cell membrane and then resulted in damage of cell membrane (Santos et al. 2013). For example, polymyxin is an antibiotic, which destroys the protective covering of bacterial cell membrane. Polymixin antibiotics consist of hydrophobic tail part with the positive charge containing cyclic peptide; these special arrangements can interact/bind the cell membrane and lead to destroy the Gram-negative bacterial membranes. When the nanomaterials come in contact with the cell membrane; it leads to somehow change in their cell permeability and destroy the cell. Leroueil et al. nicely explained the cell membrane damage; when the nanomaterials come in contact to the cell membrane, it leads to "hole" or "pore" formation in the cell membrane (Aruguete et al. 2013). However, the extent of cell membrane damage totally depends on the nanoparticle size, charge, and morphology (Aruguete et al. 2013). Sometimes, nanomaterials bind with bacterial cell membrane through specific proteins. For example, silver nanoparticles (AgNPs) can only bind the sulfur-containing protein. In some of the literatures, it was mentioned that when nanomaterials bind with cell membrane either directly or indirectly, cell damage occurred by the formation of reactive oxygen species (ROS). The details of ROS mediated cell damage are discussed in the next section.

1.1.2.2 Release of Compounds/Metal Toxic to the Bacterial Cell

In different way, when nanomaterials interact with bacterial cell, the metal ions or some compounds have been released from nanomaterials, which can bind the various functional groups of proteins present in bacteria. For example, silver nanomaterials release the silver ion (Ag^+), which binds the functional group of protein in bacteria. The antimicrobial activity of silver nanomaterials is highly particular for Gram-negative bacteria like *E. coli*, where silver ion inhibits the replication of bacterial deoxyribonucleic acid (DNA) and leads to their damage and cell death (Aruguete et al. 2013). Sometimes, the released Ag^+ get precipitated in the form of silver chloride (AgCl), after reacting with chloride ion, as a consequence stops the cell respiration in cytoplasm in the cell membrane, which also leads to cell death. Similarly, Cd^{2+} and Zn^{2+} binds with sulfur-containing protein in cell membrane leads to their damage or destruction.

1.1.2.3 Role of Reactive Oxygen Species (ROS) in Cell Damage

ROS are chemically reactive oxygen-based species of different type like superoxide, peroxide, hydroxyl radical, singlet oxygen, and triplet oxygen. Reduction of molecular oxygen (O_2) produces superoxide ($^{\bullet}O_2^-$), which acts as a precursor for generation of most of the other reactive oxygen species. Oxygen is the potent oxidizing agent and it is the best electron acceptor during respiration (Aruguete et al. 2013). The ground state of oxygen molecule is the triplet oxygen (or $^3O_2$) and triplet

oxygen can be exceptionally toxic for cell membranes. Singlet oxygen ($^1O_2$) is also toxic for bacteria but less toxic than triplet state oxygen. According to the literature, a wide range of nanomaterials can generate reactive oxygen species (ROS), which leads to the catastrophic failure of many biological systems like different types of protein, deoxyribonucleic acid (DNA), and ribonucleic acid (RNA). For example, TiO_2, SiO_2, ZnO, Cu, and silver nanomaterials can catalyze the generation of ROS in the presence of light (Santos et al. 2013; Din et al. 2017). Nature also generates low concentrations of ROS to defend themselves against the formation or growth of bacteria on them (Santos et al. 2013). In reverse, to fight against these ROS, bacteria generate some enzymes like superoxide dismutase, which may be able to neutralize the oxidative stress or effect of ROS. However, based on the literature, generation of ROS through nanomaterials is the best possible mechanism to kill bacterial cell.

1.1.2.4 Obstacle in Electron Transport and Protein Oxidation

In general, the metal ions delivered from nanomaterials have positive charge, while the bacterial cell membrane carries negative charge. Till now clear mechanism is not known, but from the literature, it can be concluded that metal ions can induce the membrane-bound respiratory enzymes as well as induce the efflux bombs ions leading to cell death (Chiriac et al. 2016). The pictorial representation of nanomaterial and bacterial cell interaction is also shown in Fig. 1.2.

In this section, we have discussed the probable mechanism on how the antibacterial agent actually works to stop the growth of bacteria or kill them. Now comes the next important point; how to measure the antibacterial activity of any agent. In the next section, we have discussed the most commonly employed assay/methods/techniques reported in the literature to measure the ability of any antibacterial/antimicrobial agent.

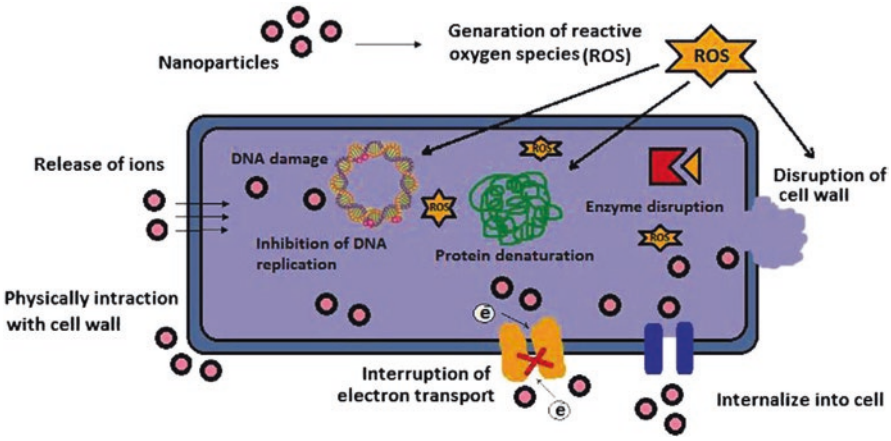

Fig. 1.2 Pictorial representation showing antimicrobial activity of nanomaterials (Chiriac et al. 2016)

1.2 Essay for Measuring the Antimicrobial Activity of Nanomaterials

The evaluation of activity of nanomaterials as an antimicrobial agent needs some experimental methods, which will determine the bacteria sustainability, after the nanomaterials have been subjected to them. Several methods have been discovered to measure the antimicrobial activity of nanomaterials like optical density or OD measurement study, cell counting method, crystal violet staining, etc. In general, the techniques were applied against Gram-negative and Gram-positive bacteria (Seil and Webster 2012). In this section, we have discussed the general and most popular methods used to determine the antimicrobial activity of nanomaterials.

1.2.1 Susceptibility of Nanomaterials Toward Microorganisms

As a foremost step, susceptibility assays are performed to access the responsiveness or sensitivity of nanomaterials toward microorganisms. In this regard, determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) are the most popularly used methods to detect the susceptibility of nanomaterials toward microorganisms. MIC is actually the lowest concentration of antibacterial agent (expressed in μg/L or mg/L) required to inhibit the growth of bacteria in given time interval (usually overnight). However, MBC is the lowest concentration of antibacterial agent required to kill 99.9% of bacteria in a given time period. The graphical representation showing the difference between these two terms is shown in Fig. 1.3. Commonly, to evaluate the MIC and MBC, dilution method is used. However, susceptibility can be studied through disc diffusion method also, which is another popular method to access the effect of nanomaterial on the microorganisms.

1.2.1.1 Dilution Method

In order to determine the efficiency of nanomaterials toward bacterial cell, broth dilution method is the most popular one. In this method, different concentrations of nanomaterials were subjected to the bacterial cell and kept for incubation at 37 °C for 24 h (Balouiri et al. 2016; Karaman et al. 2017). The bacterial cell in broth medium is taken as positive control (i.e., without nanomaterials), while negative control has only broth medium. As we know, MIC is the lowest concentration of nanomaterial required to visually inhibit almost 99% growth of bacterial cell. Here, MIC is determined by observing the visual turbidity appearance in the vial containing cells and nanomaterials.

Similarly, for MBC determination, a small amount (around 50–100 μL) of suspension was taken from each tube (used for MIC determination), which does not

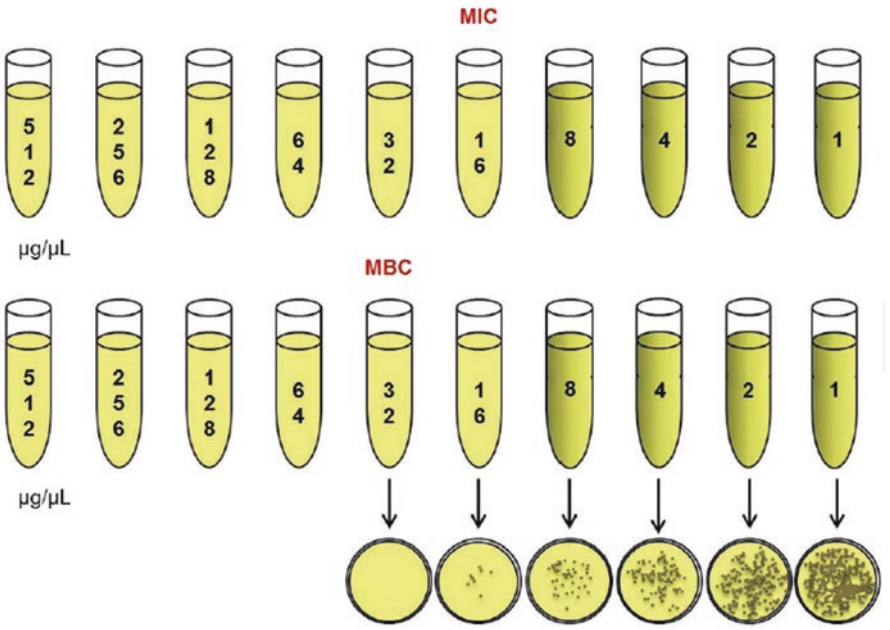

Fig. 1.3 Schematic representation showing minimum inhibitory concentration (MIC) versus minimum bactericidal concentration (MBC) (Karaman et al. 2017)

showed any visible bacterial growth and seeded in agar plates and kept for incubation at 37 °C for additional 24 h. The MBC was determined by observing the presence or absence of bacterial growth in each agar plate (Balouiri et al. 2016).

1.2.1.2 Disc-Diffusion Method

Starting from 1940, disc-diffusion method has become an official method in clinical laboratories to study the antimicrobial susceptibility (Balouiri et al. 2016). In this method, firstly, on the Petri dish, agar coated bacterial strain are homogeneously spread by the help of cotton bud or spatula. After that, a disc of filter paper (about 4–5 mm diameter) containing nanomaterials of different concentrations are place in the Petri dish. The dishes were closed and sealed to keep it for incubation at suitable condition. From filter paper, nanomaterials diffuse to the bacterial cell and kill them, depending on their efficiency and concentrations. The spherical region around the filter paper has been measured as zone of inhibition, which provides the efficacy of nanomaterials toward bacterial cell.

1.2.2 Methods for Quantification of Antibacterial Activity

The method discussed in the previous sections is devoted to study the visual changes caused by the nanomaterials. However, to quantify the percentage of cell killing, other methods are deployed.

1.2.2.1 Optical Density (OD) Measurement

Optical density or OD measurement technique is the most common method to determine the bacterial cell concentration. Here, the bacterial cell concentration was monitored by using UV-visible spectrophotometry. From this method, the degree of proliferation can be predicted by determining the cell concentration of bacteria at different time intervals. In this technique, the light is passed in the bacteria cell or sample and then spectrophotometer record the corresponding optical density. For comparison, the same experiment has been done with standard sample, whose bacteria cell concentration is known to us. If the sample penetrated less light, it means bacteria cell concentration is high in the sample, with respect to the standard sample or vice versa. Similarly, using the standard calibration curve and regression equation, the bacteria cell concentration can also be determined. This technique is very simple in use and therefore widely applied to explore the effect of nanomaterials on the bacteria. Some of the advantages and disadvantages of this technique are summarized in Table 1.1 (Seil and Webster 2012).

Table 1.1 Some advantage and disadvantage of commonly used methods for quantification of antibacterial activity of nanomaterials [reproduced from reference (Seil and Webster 2012)]

Name of the method	Advantages	Disadvantages
Optical density (OD) measurement	Fast, easy to handle, no chemical required	Spectrophotometer instrument is required, low accuracy
Cell counting method	Accuracy is high	Costly instrument required
Spread-plate colony counts	Accuracy is high	Can't counts cell size of CFU, time taking process, required disposal materials
Crystal violet staining	Identify and counts biofilm formation	Spectrophotometer instrument is required and not applicable for planktonic bacteria cell growth
Live/dead cell staining and imaging	Offers imagining of sample surface	Cost effect due to reagents required, fluorescent plate reader is required
Tetrazolium salt reduction	Counts cell viability on the surfaces and also in solution	Spectrophotometer instrument is required, costly reagents required

1.2.2.2 Cell Counting Method

For counting the cell number in a liquid suspension of bacteria, the conductivity of the solution is also measured sometimes (Seil and Webster 2012). From this method, the presence of cell density and their size distribution can be exactly determined.

1.2.2.3 Spread-Plate Colony Counts

In another method, colony-forming units (CFUs) can be calculated by the help of microscopes. In this method, the bacteria cells were monitored on agar plate. From this method, a comparison can be made between the bacterial cell incubated agar plates, with and without nanomaterials. This technique also has some advantages and disadvantages, which are portrayed in Table 1.1 (Seil and Webster 2012).

1.2.2.4 Crystal Violet Staining

For the estimation of formed bacteria colony biofilm, hexamethyl pararosaniline chloride (which is crystal violet color) can be used as a staining agent. Crystal violet is a cost-effective and popular dye, which is used to measure the effect of nanomaterials on the total biomass of bacterial film. This dye can bind to Gram-negative bacteria as well as extracellular polymeric substance like polysaccharides (Seil and Webster 2012). After staining was performed, the adsorbed dye will be eluted in different types of solvents like ethanol, methanol, etc. The dye eluted in the solvent can be measured by any spectrophotometric methods and will be directly proportional to the biomass of the bacterial film.

1.2.2.5 Live/Dead Cell Staining and Imaging

Confocal fluorescence imaging of bacterial cell is nowadays very popular to measure the concentration of dead and live bacteria after the treatment of nanomaterials. For this, Syto® 9 green fluorescent nucleic acid stain with excitation 480 nm and emission 500 nm can be used for detection of both dead and live cells, while propidium iodide with excitation 490 nm and emission 635 nm can be used for the identification of only dead cells (Seil and Webster 2012). Sometimes the combination of these two is also used to the individual cell strains, to observe the dead and living cells.

1.2.2.6 Tetrazolium Salt Reduction

From this technique, different tetrazolium salts are used to measured cell viability using spectrophotometry. Different tetrazolium salts such as MTS (3-[4,5-dimethyl thiazol-2-yl]-5-[3-carboxymethoxyphenyl]-2-[4-sulfophenyl]-2Htetrazolium),

XTT (2,3-bis-[2-methoxy-4-nitro-5-sulfophenyl]-2H-tetrazolium-5-carboxanilide), and MTT (3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) are used for determination of cell viability in the presence or absence of nanomaterials. On the high popularity of MTT use in this method, the detection method is popularly called as MTT assay. In this process, the tetrazolium salts get reduced to different color formazan derivatives, when came in contact to the dehydrogenase and reductase enzymes present in the living cells. The formation/conversion of formazan derivatives directly depend on the presence of viable cells, which offered the cell concentration. The common advantages and disadvantages of this method are portrayed in Table 1.1 (Seil and Webster 2012).

Till the point, we have discussed how the effect of nanomaterials on the bacterial cell can be observed or detected. We have also discussed the possible and probable mechanism for bacterial cell killing. Now, in the next sections, we have focused on the nanomaterials used or reported in the literature and showed high antibacterial properties.

1.3 Role of Nanomaterials as Antimicrobial Agent

1.3.1 The Ancient Era

It is not like nanomaterials are the only one class of compounds and have ability to kill the bacterial cell or retard their cell growth. Prior to that, when nanomaterials were not in picture, a wide number of organic compounds have been used as an antimicrobial agent. For example, Janeczko et al. have synthesized naphthalene-1,4-dione derivatives and checked their antimicrobial activity against eight bacterial cells such as *Proteus*, *Enterobacter*, *Staphylococcus*, *Pseudomonas*, *Escherichia*, *Klebsiella*, *Salmonella*, and *Enterococcus* (Janeczko et al. 2016). All the synthesized derivatives of naphthalene-1, 4-dione has shown pronounced antimicrobial activity with minimum inhibition concentration (MIC) in the range of 5.8–500 μg/mL. Raimondi et al. have prepared various types of pyrrolomycin compounds by microwave-assisted methods and tested their antimicrobial properties against both Gram-positive and Gram-negative bacteria (Raimondi et al. 2019). Recently, thiouracil derivatives having triazolo-thiadiazole compounds exhibited promising antimicrobial properties toward the Gram-negative and Gram-positive bacteria, as reported by Cui et al. (2017). Sekhar and co-workers have prepared some heterocyclic compounds such as 1,3,4-thiadiazoles, pyrimidinyl 1,3,4-oxadiazoles, and 1,2,4-triazoles and tested their antimicrobial and antifungal activity (Sekhar et al. 2018). All the prepared compounds have shown very good antimicrobial and antifungal activity, due to the presence of 1,3,4-thiadiazole backbone in their structures. Although various organic compounds exhibited promising antimicrobial activity against large number of bacteria, the major disadvantage behind these compounds is their large particle size and complicated/tedious synthesis approach. This leads to

low surface area to volume ratio, more cost, and difficulty in their separation from their pure form. Other than this aspect, more importantly, the bacterial cells have developed resistance toward these antimicrobial agents, and to overcome this effect, their high dose is required to cure the disease, which leads to hostile side effects.

1.3.2 Why Nanomaterials Have Replaced the Ancient Antimicrobial Agents?

To overcome drawbacks of conventional antimicrobial agent, nanomaterials came in light and well explored as antimicrobial agent, owing to their easy synthesis and purification, affordable cost, eco-friendly nature, small size, and high surface to volume ratio (which is the most prominent factor). In the last few decades, nanotechnology has been developed very rapidly as well as successfully in the field of antimicrobial treatment. Nanoscale structured (particle size 1–100 nm) materials possess high surface area to volume ratio, that is why it has unique physical, chemical, electrical, mechanical, magnetic, electro-optical, magneto-optical, and optical properties entirely different from their corresponding bulk materials (Whitesides 2005). Having large surface to volume ratio and possessing high reactivity, when nanomaterials came in contact with bacterial cell, then large amount of cell get in contact with these nanomaterials, leads to easy destruction of cells and finally death. Because of their unique features and properties, nanomaterials are also called as wonder of modern medicine. Different viruses, bacteria, and fungi can be stopped or killed within a few minutes, after treatment with nanomaterials. This credit can be given to their small size, due to which nanomaterials can easily enter/penetrate into the cell membrane and start their action within small time span (Haghi et al. 2012; Prasad et al. 2018). And this can be the reason for popularity of nanomaterials as antimicrobial agents.

1.4 Different Class of Nanomaterials Used as an Antimicrobial Agent

In this section we have summarized some of the nanomaterials which are used as an antimicrobial agent and their probable working mechanism. The most popular nanomaterials as antimicrobial agents come from the metal nanoparticles. The nanomaterials/nanoparticles of Ag, Pt, Au, and Cu and metal oxides like Ag_2O, SiO_2, TiO_2, MgO, ZnO, CaO, CuO, and Fe_2O_3 have shown their antimicrobial activities very successfully in various literatures (Lemire et al. 2013). Some of the recent ones are discussed in the next section.

1.4.1 Antimicrobial Properties of Silver-Based Nanomaterials

From the very old times, silver is used as antimicrobial agent, while from the last few decades, their nanomaterials came into picture and were very popularly used in recent times. Koduru et al. have nicely explained the function of silver nanoparticles (AgNPs) in microorganisms or bacteria (Patil and Kim 2017). According to them, AgNPs or silver-based nanomaterials are able to inhibit the growth of microorganisms. Although exact mechanism is still under debate, possible mechanism involves two stages. At first the AgNPs or silver-based nanomaterials were fabricated using different active organic or bioorganic molecules. The use of organic and bioorganic molecules in their synthesis can accelerate the antimicrobial activity of resulted nanomaterials, which inhibit the cell growth. In second step, silver nanomaterials enter into the bacterial cell, which totally depends on the size, shape, and surface chemistry of the entering agent. Silver nanomaterials give silver ion (Ag^{+}) by oxidative dissolution of silver nanomaterials (present Ag^{0}). These silver ions have affinity to strongly bind with marpapto groups of enzymes, organic functional groups, proteins, and DNA of bacteria cell via formation of covalent bond between silver ions and sulfur (Ag-S), which have bond energy 65 kcal/mol. The strong binding between Ag^{+} and bacterial cell destroys the bacteria DNA to inhibit the bacterial replication and finally kill the cell (Li et al. 2010).

Chernousova and Epple have reported that with changing morphology or shape of the particles, the interaction between the nanomaterials (silver nanomaterials) and bacterial protein can be changed (Chernousova and Epple 2013). The silver nanomaterials were also able to generate the reactive oxygen species (ROS), which can destroy the various biochemical systems in bacteria (Chernousova and Epple 2013). It is already evidenced that the high-level ROS have been detected by applying silver nanomaterials in the bacterial cell, which leads to high oxidative stress and damages the bacterial protein (Patil and Kim 2017). Sharma et al. have investigated the antimicrobial activity of silver nanoparticles with the nanomolar and micromolar concentration, whereas micromolar concentration showed better result, i.e., antimicrobial activity than nanomolar concentration (Sharma et al. 2009). This group also reports the role of silver ions toward antimicrobial applications. According to the literature, firstly, silver ions generated from silver nanomaterials get chemisorbed on the surface of silver nanomaterials. Therefore, surface concentration of silver ions in silver nanomaterials largely reflects the antimicrobial activity. After that, silver nanomaterials adsorbed on the cell membrane wall lead to prevent the cell growth and proliferation. Then, silver nanomaterials enter/penetrate into the cell membrane and as a result destroy or inhibit the function of the proteins, DNA damage and death the cell. The credit behind the cell death can be attributed to silver ions, which bind the proteins and destroy the cell membrane wall (Prasad and Swamy 2013; Aziz et al. 2019).

According to other literature, firstly, silver nanomaterials come in contact with the cell wall and after that gradually release the silver ions from the silver nanomaterials and accordingly produced ROS by several biochemical processes (Patil and Kim 2017). Finally, destroy or inhibit the function of proteins, enzymes in

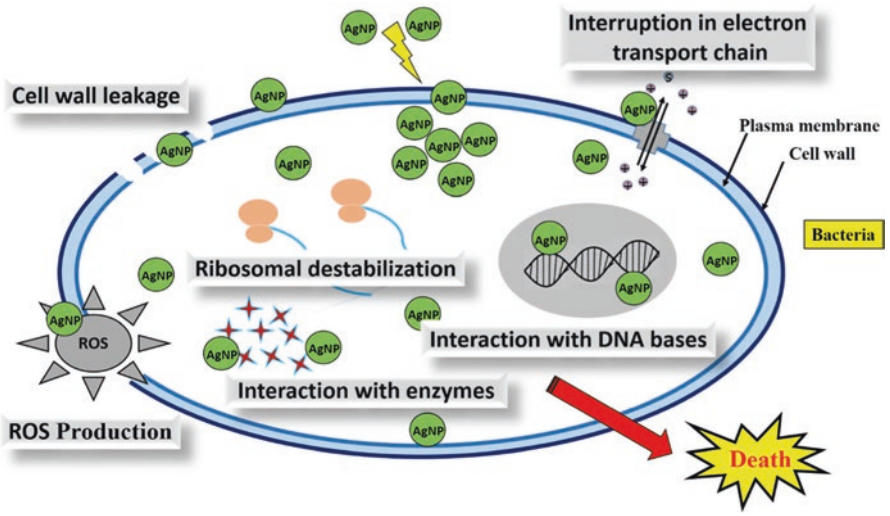

Fig. 1.4 Schematic representation showing antimicrobial activity of AgNMs (Patil and Kim 2017)

cytoplasma and lead to cell death. The role of silver nanomaterials in bacteria cell is shown in Fig. 1.4 (Patil and Kim 2017). Some of the synthesized silver nanomaterials from different precursors, its shape, size, and antimicrobial activity toward particular bacterial cell are summarized in Table 1.2 (Ajitha et al. 2016; Ibrahim 2015; Dhand et al. 2016; Hassanien and Khatoon 2019; Alfuraydi et al. 2019; Varghese et al. 2017; Sulaiman et al. 2013; Padalia et al. 2015; Palanisamy et al. 2017; Rao et al. 2016; Verma and Mehata 2016; Ravichandran et al. 2016; Nzekwe et al. 2016; Jena et al. 2015).

1.4.2 Antimicrobial Activity of Zinc Oxide Nanomaterials (ZnO)

Various metal oxide nanomaterials have been used as an antimicrobial agent. But the main advantage of zinc oxide nanomaterials than the other nanomaterials is their non-toxicity, biocompatibility, and photochemical stability. Additionally, zinc oxide is listed safe material recommended by the US Food and Drug Administration to Food and Administration (Dimapilis et al. 2018). Nanosized zinc oxide nanomaterials (not more than 100 nm) have shown prominent antimicrobial properties than macro-sized nanomaterials. Due to small size (less than 100 nm), they have high surface/volume ratio which allow more interaction between the nanomaterials and bacteria cell. For the last few years, several studies have been shown that zinc oxide nanomaterials selectively destroy the bacteria and also revealed the minimum effects on the human cells (Bhuyan et al. 2015; Dimapilis et al. 2018). Antimicrobial properties of

Table 1.2 Synthesis of AgNPs using different reducing/capping agents and their antimicrobial activity

S. N.	Name of the reducing or capping agent	Shape and size	Antimicrobial activity against bacteria cell	MIC[a]	References
1.	*Sesbania grandiflora* leaf extract	Spherical and 20 nm	Gram-negative (*E. coli*, *Pseudomonas* spp.) and Gram-positive bacteria (*Bacillus* spp., *Staphylococcus* spp.), and fungi (*Aspergillus niger* subsp., *A. flavus* subsp. and *Penicillium* spp.)	2–6 μL	Ajitha et al. (2016)
2.	Banana peel extract	Spherical and 23.7 nm	Bacteria (*B. subtilis*, *S. aureus*, *P. aeruginosa*, *E. coli*) and yeast (*Candida albicans*)	1.70–6.80 μg/L	Ibrahim (2015)
3.	Seed extract of *Coffea arabica*	Spherical, ellipsoidal and 10–150 nm	*S. aureus* and *E. coli*	0.02–0.1 M	Dhand et al. (2016)
4.	Tanic acid and $C_{76}H_{52}O_{46}$	Spherical and 33.3–69.8 nm	Bacteria (*E. coli* and *Bacillus*) and fungi (*Candida albicans*)	–	Hassanien and Khatoon (2019)
5.	Sesame oil cake	Spherical and 6.6–14.80	*P. aeruginosa*, *E. coli*, and *K. pneumonia*	0.5 μg/mL	Alfuraydi et al. (2019)
6.	Seed extract of *Trigonella foenum-graecum L*	Spherical and 39.3 nm	*Staphylococcus aureus*, *E. coli*, *Klebsiella pneumonia*, *Aspergillus flavus*, *Trichophyton rubrum*, and *Trichoderma viridiae*	62.5, 125 and last three each 250 μg/mL	Varghese et al. (2017)
7.	*Eucalyptus camaldulensis*	–	*P. aeruginosa*, *E. coli*, *S. aureus*, and *B. subtilis*	–	Sulaiman et al. (2013)
8.	Matricaria chamomile plant extract	–	Bacteria (*S. aureus*, *E. coli*) and fungus (*Candida albicans*)	1–100 ppm	Padalia et al. (2015)
9.	Flower broth of *Tagetes erecta*	Spherical, hexagonal, and irregular and 10–90 nm	Bacteria (*E. coli*, *P. aeruginosa*, *S. aureus*, *B. cereus*), fungi (*Candida albicans*, *Candida glabrata*, *Cryptococcae neoformans*)	–	Palanisamy et al. (2017)

(continued)

Table 1.2 (continued)

S. N.	Name of the reducing or capping agent	Shape and size	Antimicrobial activity against bacteria cell	MIC[a]	References
10.	*Gelidium amansii*	Spherical and 27–54 nm	*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus pumilus*, *E. coli*, *Aeromonas hydrophila*, and *Vibrio parahaemolyticus*	25–100 μg	Rao et al. (2016)
11.	Extract of neem (*Azadirachta indica*) leaves	Spherical	*S. aureus* and *E. coli*	0–120 μg/mL	Verma and Mehata (2016)
12.	*Artocarpus altilis* leaf extract	Different shapes and 34–38 nm	Bacteria (*E. coli*, *P. aeruginosa*, *S. aureus*) and fungi (*A. versicolor*)	0–120 μg/mL	Ravichandran et al. (2016)
13.	$NaBH_4$	Spherical	*E. coli*, *S. aureus*, *Klebsiella* spp., *B. subtilis*	–	Nzekwe et al. (2016)
14.	Pod extract of *Cola nitida*	Spherical and 10–80 nm	*P. aeruginosa*, *K. granulomatis*, *E. coli*, *S. aureus*, *A. flavus*, *Aspergillus niger*, and *A. fumigatus*	50–150 μg/mL	Jena et al. (2015)

[a]*MIC* Minimum inhibition concentration

zinc oxide nanomaterials have been well explored against both Gram-positive bacteria and Gram-negative bacteria and also for *Escherichia coli*, *Salmonella typhimurium*, *B. subtilis*, *S. enteritidis*, *Streptococcus pyogenes*, *E. faecalis*, *Aeromonas hydrophila*, *S. aureus*, *L. monocytogenes*, *Klebsiella pneumonia*, and *P. aeruginosa* (Kumar et al. 2017). In order to demonstrate the activity of nanomaterials toward microorganism, several step mechanisms are proposed, which involves metal ion discharge/release from nanomaterials, production of ROS, cell membrane dysfunction, disturbance of electron transport, and penetration of nanomaterials into the cell membrane, which are directly involved in the cell death. The procedure of generation of ROS by zinc oxide nanomaterials is shown in Fig. 1.5 (Dimapilis et al. 2018). In addition, the zinc oxide nanomaterials have band gap of 3.28 eV, which reflects their high binding energy of 60 meV, which may also lead to their strong binding with bacterial cell (Kumar et al. 2017).

It has also been found that antibacterial property of ZnO depends on several factors. For example, in the year of 2013 Heniti and Umar investigated that how surafce area of zinc oxide nanomaterials affect the antimicrobial activity and they found propotional relationship between surface area of nanomaterials (ZnO) and antimicrobial activity, which means with increasing surface area of nanomaterials antimicrobial activities also increased and vice versa (Al-Heniti and Umar 2013). Rodrigo et al. have reported that antimicrobial activities of ZnO have been greatly affected by their size, shape, or surface morphology and surface area of the zinc

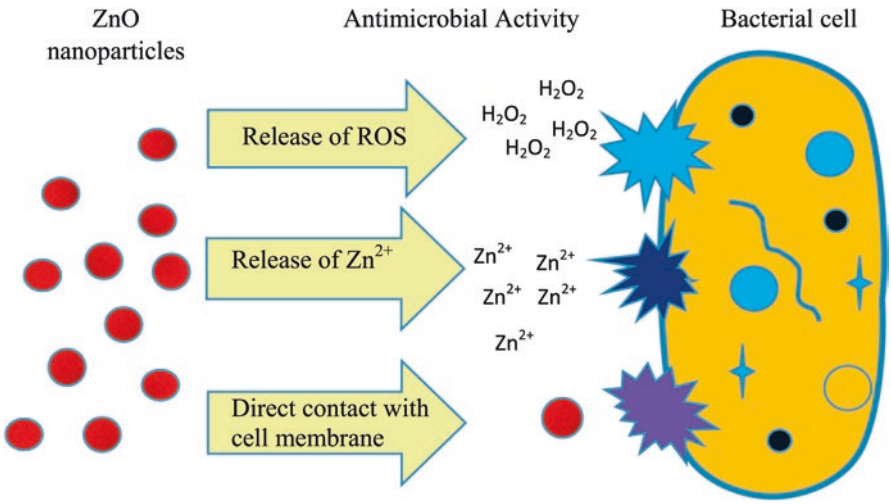

Fig. 1.5 Production of ROS and Zn2+ from ZnO nanomaterials (Dimapilis et al. 2018)

oxide nanomaterials (Rodrigo et al. 2013). Jain et al. have synthesized ZnO NPs via simple one-step hydrothermal method and used as an antimicrobial agent for the Gram-positive bacteria (such as *Staphylococcus aureus*, *Enterobacter aerogenes,* and *Bacillus subtilis*) and Gram-negative bacteria (such as *Escherichia coli* and *Aerobacter aerogenes*) (Jain et al. 2013). Authors have also studied antimicrobial activity of ZnO NPs for both the bacteria (Gram positive and Gram negative) and observed higher antimicrobial activities for Gram-positive (MIC = below 100 μg/mL) than Gram-negative bacteria (MIC = 500 μg/mL). Another research group in year 2013 prepared different morphologies of ZnO nanomaterials (nanorods and nanoflowers) by simple hydrothermal method and used as antimicrobial agent against *Staphylococcus* and *E. coli* (Talebian et al. 2013). The antimicrobial activity has been found higher for nanoflower-shaped ZnO than other shapes of nanomaterials against *E. coli* bacteria. In addition, several other methods have also been reported for the synthesis of various morphologies of ZnO nanomaterials such as nanorods, nanospheres, nanoflowers, thin film, etc. Some of the ZnO nanomaterials along with their antimicrobial activities are summarized in Table 1.3 (Stankovic et al. 2013; Shinde et al. 2014; Aal et al. 2015; Liu et al. 2009; Janaki et al. 2015; Ramesh et al. 2015; Umar et al. 2013; Ambika and Sundrarajan 2015; Huang et al. 2008; Raghupathi et al. 2011; Premanathan et al. 2011; Nair et al. 2009; Padmavathy and Vijayaraghavan 2008; Dwivedi et al. 2014; Kumar et al. 2013).

Table 1.3 Synthesis of ZnO NPs using different methods and their antimicrobial activity

S. N.	Method of preparation	Shape of ZnO NPs	Antimicrobial activity against bacteria cell	Minimum inhibition concentration (MIC)	References
1.	Hydrothermal method	Prismatic, nanorods, nanospheres and nano-ellipsoid	*E. coli* and *S. aureus*	Nanospheres showed highest antimicrobial activity against both the bacteria	Stankovic et al. (2013)
2.	Microwave method	Microspheres	*E. coli* and *S. aureus*	25 μg/mL	Shinde et al. (2014)
3.	Hydrothermal method	Nanotubes	*A. baumannii*, *E. coli*, *K. pneumonia*, *P. mirabilis*, *P. aeruginosa*, *S. typhi*, *B. subtilis*, *M. luteus*, *S. aureus*, MRSA, *S. epidermidis*, and *S. pneumonia*	0.55 ± 0.04, 0.45 ± 0.04, 0.55 ± 0.04, 0.45 ± 0.04, 0.55 ± 0.04, 0.65 ± 0.04, 0.65 ± 0.04, 0.75 ± 0.04, 0.75 ± 0.04, 0.75 ± 0.04, 0.60 ± 0.04, and 0.60 ± 0.04 μg/mL, respectively.	Aal et al. (2015)
4.	–	Nanopowders	*E. coli*	3 μg/mL	Liu et al. (2009)
5.	Green synthesis using ginger rhizome extract	Nanoparticles	*K. pneumonia* and *S. aureus*	–	Janaki et al. (2015)
6.	Green synthesis using *Solanum nigrum* leaf extract	Nanoparticles	*S. aureus*, *S. paratyphi*, *V. cholera*, and *E. coli*	–	Ramesh et al. (2015)
7.	Solvothermal method	Nanoflowers	*E. coli*	25 μg/mL	Umar et al. (2013)
8.	Green synthesis using *Vitex negundo* extract	Nanoparticles	*E. coli* and *S. aureus*	–	Ambika and Sundrarajan (2015)
9.	Precipitation method	Different shape	*S. agalactiae* and *S. aureus*	–	Huang et al. (2008)

(continued)

Table 1.3 (continued)

S. N.	Method of preparation	Shape of ZnO NPs	Antimicrobial activity against bacteria cell	Minimum inhibition concentration (MIC)	References
10.	Solvothermal method	Nanoparticles	*S. aureus*, *S. epidermidis*, *S. pyogenes*, *E. faecalis*, *B. subtilis*, *E. coli*, *P. vulgaris*, and *S. typhimurium*	–	Raghupathi et al. (2011)
11.	Wet chemical method	Nanoparticles	*E. coli*, *P. aeruginosa*, and *S. aureus*	500, 500, and 125 μg/mL	Premanathan et al. (2011)
12.	Wet chemical method	Nanoparticles	*E. coli* and *S. aureus*	–	Nair et al. (2009)
13.	Precipitation method	Nanoparticles	*E. coli*	–	Padmavathy and Vijayaraghavan (2008)
14.	Wet chemical method	Nanoparticles	*Pseudomonas aeruginosa*	–	Dwivedi et al. (2014)
15.	Solution method	Nanoflowers	*Pseudomonas aeruginosa*	25 μg/mL	Kumar et al. (2013)

1.4.3 Antimicrobial Activity of Titanium Oxide (TiO_2) Nanomaterials

For the last few years, TiO_2-based nanomaterials or NPs have shown broad range of antimicrobial activity against the various Gram-positive as well as Gram-negative bacteria cell. Presently TiO_2 NPs have become the first choice in various fields and industries like food industry, cosmetics industry, medical field, waste water treatment, drug delivery, etc. TiO_2 NPs have distinctive photocatalytic property and small particles size which create the TiO_2 NPs a model antimicrobial agent against various bacteria cells (Fernando et al. 2018). The action mechanism of TiO_2 NPs is slightly different than the silver or zinc oxide nanomaterials, due to unique photocatalytic properties of TiO_2 NPs. Bacteria cells get damaged by the light, which is coming from TiO_2 NPs (Fernando et al. 2018). After that TiO_2 NPs get oxidized to form reactive oxygen species, which can destroy the cell membrane.

Some of the literatures showing the role of TiO_2 NPs as antimicrobial agent are discussed below. For example, Haghi et al. have synthesized TiO_2 NPs and checked their antimicrobial activity against *E. coli* bacteria using various concentrations of TiO_2 nanomaterials (Haghi et al. 2012). It was found that with increase in concentration of TiO_2 NPs, their antimicrobial activity also increased. Similarly, Saraschandra et al. have prepared TiO_2 NPs coated with high-density polyethylene

by sol-gel followed by ultrasonication method (Saraschandraa et al. 2013). The prepared NPs show good antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*.

1.4.4 Copper Nanomaterials as an Antimicrobial Agent

Copper (Cu) is a key element for metabolism of animals as well as plant cells. More than 30 proteins contain copper element/ion in their composition; however, almost every living organisms also contain trace amount of copper element. For the last few years, copper nanoparticles (CuNPs) have shown ideal biological application in low cost. Recently, copper and copper-based nanomaterials have shown their potential as antimicrobial activity against various bacteria cells (Holubnycha et al. 2017). For example, Rafi et al. have reported copper sulfate, copper hydroxide, and aqua complex of copper as an antimicrobial agent (Raffi et al. 2010). According to the American Environmental Protection agency, copper has been listed at the top for their antimicrobial activity against bacteria cell (Prado et al. 2012). Sometimes, copper nanomaterials have shown higher antimicrobial activity in comparison to costly and popular noble metal-based nanoparticles like AgNPs (Holubnycha et al. 2017).

The action mechanism of copper nanomaterials possesses multiple steps, which includes electrostatic interaction/attraction between the copper nanomaterials and bacterial cell. As CuNPs itself have positive charge on the surface and bacteria cell contains negative charge, results in their strong binding with cell membrane, which later on results in protein denaturation. Sometimes, CuNPs bind with cell DNA also through the binding interaction between phosphorous and copper (Mahmoodi et al. 2018). It is also reported in some of the literature that CuNPs also lead to generation of ROS which lead to cell membrane destruction, protein oxidation, and DNA denaturation, which finally kill the cell (Din et al. 2017; Yadav et al. 2017). The corresponding mechanism is shown in Fig. 1.6 (Din et al. 2017). Bogdanovic et al. have prepared CuNPs having size 5 nm and tested their antimicrobial activity against different bacteria cell such as Gram-negative bacteria (*Escherichia coli*) and Gram-positive bacteria (*Staphylococcus aureus* and *Candida albicans*) (Bogdanovic et al. 2014). Authors calculated the percentage reduction in their growth after treatment of CuNPs and found 99% reduction. The reduction in cell growth has been calculated following the equation given below:

$$R(\%) = \frac{C_o - C}{C_o} * 100 \tag{1.1}$$

where, R, C_o, and C indicate the percentage reduction of microbial growth, initial number of microbial colonies (CFU), and number of microbial colonies, after treatment with CuNMs, respectively. Holubnycha et al. have synthesized copper

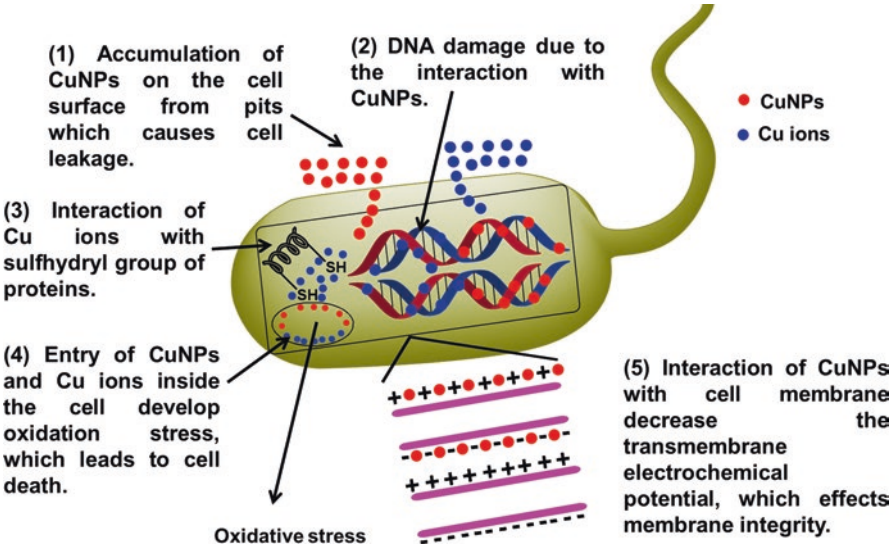

Fig. 1.6 Mechanisms showing antimicrobial properties of copper nanomaterials (Din et al. 2017)

nanomaterials with particle size in the range of 15–20 nm by chemical reduction method (Holubnycha et al. 2017). The prepared copper nanomaterials along with different concentration of chitosan solution (molecular weight 200 kDa and 500 kDa) were tested against *E. coli* and *S. aureus* (Holubnycha et al. 2017). Interestingly authors observed that copper nanomaterials with 200 kDa chitosan show good antimicrobial activities, but copper nanomaterials with 500 kDa chitosan solution have less or no antimicrobial activity against the bacteria cell (*E. coli* and *S. aureus*). It is assumed that copper nanomaterials with low molecular weight chitosan solution (200 kDa) have shown good antimicrobial activity because of their strong binding with mRNA block present inside the cell membrane. However, high molecular weight chitosan solution (500 kDa) probably made strong binding with copper nanomaterials and therefore not get free to bind with bacterial cell and showed no or decreased antimicrobial activity.

1.4.5 Carbon-Based Nanomaterials as an Antimicrobial Agent

Carbon is the most important element in the world and similarly their nanomaterials are also the most demanded material. Carbon nanostructures exist in mainly three dimensions: (1) zero dimensional, fullerene; (2) one dimensional, carbon nanotube; and (3) two dimensional, graphene. In 1985, Kroto et al. first discovered the zero dimension fullerenes (Kroto 1997). Thereafter in the year of 1991, Sumio Iijima first time discovered the carbon nanotubes (Iijima 1991). Afterward, single layer

graphene was first isolated from graphite powder by Andre Geim and Nosovelov in the year of 2014 (Novoselov et al. 2004). Presently, carbon-based nanomaterials such as graphene oxide, fullerene, carbon nanotube (mainly single-walled carbon nanotube), and activated carbon nanomaterials have been greatly used as an antimicrobial agent and show ideal antimicrobial activity against different bacteria cells. It has been well known that size and surface area of the any nanomaterials can greatly affect their antimicrobial properties. Since carbon-based nanomaterials have small size and large surface to volume ratio, they showed higher interaction with bacteria cell. Although, the antimicrobial properties of carbon based nanomaterials also depend on the composition of the nanomaterials, functionalization of carbon based nanomaterials and type of the bacteria (Dizaj et al. 2015).

If we discuss about their mode of action, in the literature, multiple-step mechanisms have been involved for the bacteria cell death. Carbon-based nanomaterials mainly destroy the cell membrane by the oxidative stress. But present studies showed that the physical interaction between the carbon-based nanomaterials and bacteria cell are the primary mechanism rather than oxidative stress (Dizaj et al. 2015). Herein, we have discussed the antimicrobial properties of carbon-based nanomaterials as well as their mode of action.

1.4.5.1 Fullerene

Fullerenes are the allotrope of carbon with football-like shape. Fullerenes have been used as a potent antimicrobial agent against various bacteria cell like Gram-negative bacteria (*E. coli*) and Gram-positive bacteria (*Streptococcus* spp. and *Salmonella*). Several studies have suggested that fullerene and their derivative can destroy the cell membrane by damaging the respiratory system by affecting the oxygen uptake (Deryabin et al. 2014). It has been also observed that with altering fullerene concentration (i.e., from low to high level) leads to change in oxygen uptake also, i.e., from low to high. According to the literature, fullerenes have hydrophobic surface, which can easily bind with the membrane cells and results in cell disruption (Deryabin et al. 2014). Fullerene derivatives can be synthesized with any charge (i.e., positive or negative) or no charge, i.e., neutral charged, but among the three classes of fullerene, only cationic charged showed potent antimicrobial activity against *E. coli* and *Shewanella oneidensis*, while anionic fullerene derivatives do not have any antimicrobial properties. Because, fullerene derivatives bearing cationic charge can interact with negatively charge bacteria cell, while other failed to do so (Tegos et al. 2005). Deryabin and co-workers (2014) have reported the antimicrobial activity of two water-soluble fullerene derivatives (Deryabin et al. 2014). They have prepared deprotonated carboxylic acid and protonated amine functional group containing fullerene derivative using organic linkers and tested their antimicrobial activity against *E. coli* bacteria. It was found that fullerene derivative with protonated amine exhibited potent antimicrobial activity, but deprotonated carboxylic containing fullerene derivative did not show any antimicrobial activity. Finally authors have concluded that the protonated amine containing fullerene derivatives possesses

positive charge which can interact with negatively charged *E. coli* bacteria, but another one did not able to develop such kind of interaction. Additionally, it is well known that solubility of fullerene derivatives increases by functionalizing hydrophilic functional group and soluble fullerene can also be used in photodynamic therapy as a photosensitizer's agent, reported by Lu et al. (2010). Moreover water-soluble fullerene and its derivative easily reduced by the biological reducing agent lead to generate superoxide, which can destroy the microbial cells (Lu et al. 2010). In year 2005, Tegos et al. have prepared fulleropyrrolidinium by irradiation and investigated their antimicrobial activity. The fullerene-based nanomaterial showed 99% death of different bacterial and fungal cells (Tegos et al. 2005). Similarly, Cataldo and Da Ros have also prepared fullerene derivative, i.e., by sulfobutyl fullerene photoirradiation, and used them as an antimicrobial agent against bacteria cell (Cataldo and Da Ros 2008).

1.4.5.2 Carbon Nanotubes (CNTs)

Carbon nanotubes are the nanosized hollow cylinder-shaped arrangement of carbon atoms. CNTs are classified in two types, i.e., single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs). However, SWCNTs are able to easily penetrate into the bacteria cell, as consequence showed potent antimicrobial applications in comparison to the MWCNTs. In 2007, Kang et al. first time used SWCNTs for antimicrobial applications and found as an ideal antimicrobial agent against *E. coli* bacteria (Kang et al. 2007). The same group in the year of 2008 prepared both SWCNTS and MWCNTs and tested their antimicrobial activity against *E. coli* bacteria (Kang et al. 2007). They found that SWCNTs were more toxic toward bacterial cells than MWCNTs; as a result SWCNTs showed better antimicrobial activity against *E. coli* than MWCNTs. They also reported that it was the direct contact between the CNTs and bacteria cell which affected the cell membrane, metabolism process, and also the surface morphology of *E. coli*. The small size of SWCNTs is able to easily penetrate into the cell membrane and their large surface area helps to provide superior interaction.

In other study, Liju and co-workers have prepared hydroxyl and carboxylic functional group modified SWCNTs and MWCNTs and tested their antimicrobial activity against Gram-positive and Gram-negative bacteria (Yang et al. 2010). They have found that SWCNT-OH and SWCNT-COOH exhibited strong antimicrobial activity toward both Gram-positive and Gram-negative bacterial cell, but MWCNT-OH and MWCNT-COOH did not exhibit any antimicrobial activity. Arias et al. have also tested the antimicrobial activity of different length SWCNTs and used mainly three different lengths, i.e., less than 1 μm, 1–5 μm, and 5 μm (Arias and Yang 2009). It was found that the SWCNTs with longest size showed strong antimicrobial activity than the others. It may be because longer-length SWCNTs can effectively aggregate with bacterial cells, while short-length SWCNTs get aggregated to each other but not to the bacterial cell. Dong and co-workers prepared SWCNTs dispersed in various surfactants like sodium dodecyl sulfate, sodium cholate, and sodium dodecyl

benzene sulfonate by simple ultrasonication and tested their antimicrobial activity against *E. coli*, *Salmonella enterica*, and *Enterococcus faecium* (Dong et al. 2012). They found better antimicrobial activity against above bacterial cells using SWCNTs dispersed in sodium cholate and also found that antimicrobial activity increased with increase in the concentration of SWCNTs.

1.4.5.3 Graphene Oxide (GO)

Graphene is an allotrope of carbon with hexagonal structure. Graphene oxide is usually prepared from graphite using strong oxidizing agent. Graphene oxide has been greatly used in various fields such as waste water treatment, medical diagnosis, drug delivery, sensing, etc. From the last few years, graphene oxide has showed their potent antimicrobial activities against bacteria cells. Several literatures studied showed that direct contact between graphene and graphene oxide with bacteria cell resulted in membrane stress and their killing (Dizaj et al. 2015). Akhavan and Elham have prepared graphene oxide and tested their antimicrobial activity against Gram-positive and Gram-negative bacteria cells (Akhavan and Ghaderi 2010). They have found that bacteria cells were damaged by the direct contact between bacteria cells and graphene oxide nanosheets. Gurunathan and co-workers prepared graphene and reduced graphene oxide and tested the antimicrobial activity against *S. aureus* bacteria (Gurunathan et al. 2012). They found better antimicrobial activity, which suggested that the bacterial cell killing mechanism proceeds through direct contact between the bacteria cells and sharp edge of the graphene and reduced graphene oxide.

In the year 2014, Karimnezhad and co-workers have synthesized functionalized graphene oxide such as graphene oxide-chlorophyllin-Zn and graphene oxide-chlorophyllin and tested their antimicrobial properties against *E. coli* (Azimi et al. 2014). They found that graphene oxide-chlorophyllin-Zn showed better antimicrobial activity than graphene oxide-chlorophyllin against *E. coli* bacteria. This is mainly due to the surface chemistry and toxicity of zinc metal, which resulted to damage the integrity of cell, followed by their killing. Yun et al. have synthesized two nanocomposites of CNTs and GO with AgNPs, i.e., CNT-Ag and GO-Ag, and studied their antimicrobial activity against Gram-positive and Gram-negative bacteria (Yun et al. 2013). Authors found that CNT-Ag nanocomposite exhibited better antimicrobial activity than GO-Ag nanocomposite. This is because the silver nanoparticles dispersed more effectively in CNT than the others.

1.4.5.4 Activated Carbon-Based Nanomaterials (ACNMs)

Activated carbon nanomaterials are the nanosized carbonaceous nanomaterials having large surface area to volume ratio and high chemical reactivity (Lakshmi et al. 2018). ACNMs are usually synthesized by hydrothermal, chemical vapor deposition and solution combustion methods (Marsh and Reinoso 2006). Actually, carbonaceous

nanomaterials are activated by various physical and chemical activation methods to form activated carbon nanomaterials. Physical activation method consists of two steps, i.e., (1) carbonization of carbon species at high temperature under inert atmosphere and (2) carbonized products are activated using activating agent like air, steam, and carbon dioxide. But in chemical methods, simple chemical reaction between the carbon precursor and chemical agents like salts, acids, and bases takes place to activate the carbonaceous nanomaterials (Nor et al. 2013). The activated carbon nanomaterials prepared through physical activation method have large surface area than the chemical methods. Activated carbon nanomaterials have been widely used as/in adsorbents (Wickramaratne and Jaroniec 2013), supercapacitors (Liu et al. 2016), catalyst (Bian et al. 2012), lithium ion battery (Peng et al. 2014), and sensor fabrication (Claussen et al. 2012). But, from the last few decades, activated carbon nanomaterials have been largely applied as antimicrobial agent. ACNMs interact with bacteria cell which resulted in cell death. The mechanism of action followed few steps: (a) inhibition of the cell wall synthesis, (b) inhibition of protein synthesis, (c) destruction of the nucleic acids replication and transcription, and (d) destruction of the cell membrane.

Zhao et al. have synthesized silver-containing activated carbon nanomaterials (Ag/ACNMs) by physical activated method from coconut shell with particle size 2–4 nm and tested their antimicrobial activity against *E. coli* (Zhao et al. 2013). Soely et al. have synthesized activated carbon from pyrolyzed sugarcane bagasse (ACPB) by physical activation methods, followed by silver loading on the activated carbon nanomaterials (AgNM/ACPB) with pore size in the range of 1.0–3.5 and higher surface area (1200–1400 m^2/g) than commercially available activated carbon nanomaterials (Gonçalves et al. 2016). Authors have tested antimicrobial activity of synthesized materials (ACPB and ACPB/AgNM) toward *E. coli* bacteria cell and found that ACPB/AgNM showed better antimicrobial activity than ACPB. Synthesis of activated carbon nanomaterials from various biowastes and their antimicrobial activity toward particular bacterial cells are summarized in Table 1.4 (Lakshmi et al. 2018; Zhao et al. 2013; Gonçalves et al. 2016; Varghese et al. 2013; Sekaran et al. 2013; Yallappa et al. 2017; Das Purkayastha et al. 2014; Shi et al. 2007; Basker et al. 2016; Saravanan et al. 2016).

1.5 Challenges of Nanomaterials in Antibacterial Treatments

Based on the literatures we have discussed in this chapter, it is very clear that nanomaterials are promising candidate toward antimicrobial treatments. But, as discussed in the chapter, the antimicrobial activity of nanomaterials depends on several parameters like their concentration, temperature, pH, etc. Similarly, having several advantages and superior performances than ancient antimicrobial agents, nanomaterials have to face several challenges to secure their top most places in antibacterial treatments and translate this technology in real clinical use. In the list of challenges, the first and foremost one is study of complete mechanism of interaction between

Table 1.4 Synthesis of activated carbon nanomaterials from various biowastes and their antimicrobial activity

S. N.	Carbon precursor	Microorganism	MIC[a]	References
1.	Coconut	*E. coli*	10^7 CFU/mL	Zhao et al. (2013)
2.	Sugarcane bagasse	*E. coli*	10^7 CFU/mL	Gonçalves et al. (2016)
3.	Kitchen soot	*S. aureus*, *S. haemolyticus*, *P. refrigere*, and *P. aeruginosa*	–	Varghese et al. (2013)
4.	Rice husk	*Bacillus* sp.	3.2×10^7 cells/mL	Sekaran et al. (2013)
5.	Groundnut shell	*B. cereus*, *E. coli*, and *C. violaceum*	–	Yallappa et al. (2017)
6.	Sandalwood bark	*P. notatum*, *B. cereus*, *E. coli*, and *C. violaceum*	–	Lakshmi et al. (2018)
7	Rapeseed oil-cake	*E. coli*, *S. aureus*, *B. cereus*, *L. monocytogenes*, *S. enterica*, *C. albicans*, *P. diminuta*, *K. pneumonia*, *M. smegmatis*	5–15, 31–62, 31–62, 31–62, 7–15, 7–15, 7–15, 7–15, 31–62 μg/mL, respectively	Das Purkayastha et al. (2014)
8.	–	*E. coli* and *S. aureus*	–	Shi et al. (2007)
9.	*Passiflora foetida*	*B. cereus*, *S. aureus*, *Enterococcus* sp., *M. luteus*, *Corynebacterium* sp., *E. coli*, *K. pneumonia*, *P. aeruginosa*, *S. flexneri*, *S. typhimurium*, *P. vulgaris*, and *A. faecalis*	–	Basker et al. (2016)
10.	Fishtail palm seeds	*S. aureus*, *S. epidermidis*, *P. aeruginosa*, *E. coli*, and *C. albicans*	–	Saravanan et al. (2016)

[a]*MIC* Minimum inhibition concentration

nanomaterials and bacterial cells. Similarly, their effect on the living organism, like living cells (i.e., normal and disease), tissues, and organs, should be studied too, to find the optimum dose as well as fastest route of administration of nanomaterials as antibacterial agent. Therefore, to make the nanotechnology applicable in real clinical field, their use in vivo condition is very much required. As we have discussed in the Sect. 1.2, the role of nanomaterials as antibacterial agent can be studied using their particles or solutions in general as in vitro condition. But to study their in vivo role, we are still not in very advanced stage. We can always agree everyone on the fact that nanomaterials and nanotechnology have lots of potential as antimicrobial agents, but it is also very clear that we are still not aware of several facts and needs a lot of things to know, prior to using these nanomaterials in real clinical field with day-to-day use.

Acknowledgement Author Declaration, Mr. Majhi and Ms. Karfa have given the major contribution in writing this book chapter along with drawing the figures and tables, taking the copyright permission, etc.

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