Chapter 7
Surface-Modified Noble Metal Nanoparticles as Antimicrobial Agents: Biochemical, Molecular and Therapeutic Perspectives

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Abstract Despite the progress of the development of antimicrobial therapeutics, the whole world is still under pressure of several microbial diseases. Antimicrobial drug development is therefore considered as one of the most practicable research works at present time. Even most of the pharmaceutical companies are investing to develop better therapeutic solutions against the life-threatening infectious diseases caused by Mycobacterium tuberculosis, Helicobacter pylori, Vibrio cholerae, Entamoeba histolytica, Plasmodium falciparum and many others. These microbial pathogens are not only a curse for human health but also a result in huge economic losses by affecting the health of economically important animals like poultry, cattle and other livestock. Considering the urgency, several effective antibiotics have been developed to combat microbial diseases and are available in the market. However, emergence of resistance against these drugs due to the maluses has created an alarming situation. In this scenario, the use of bioactive noble metal nanoparticles (silver, gold and platinum nanoparticles) has shown better therapeutic efficiency in terms of low treatment dose, less toxicity and absence of microbial resistance. Moreover, the use of several surface modifiers, coating and stabilizing agents resulted in enhancement of the bioactivity, rapid delivery and controlled drug release, improvement of biocompatibility and cytotoxicity. In this chapter, we have presented a comprehensive overview on the antimicrobial efficacy of noble metal nanoparticles along with the mechanistic insights behind their activity at the cellular and molecular level.
Keywords  Noble metal nanoparticles · Antimicrobial activity · Drug delivery · Biocompatibility · Cytotoxicity

7.1 Introduction

The human healthcare industries throughout the world are facing tremendous challenges due to the increasing emergence of resistance in pathogenic bacteria, fungi and parasites against the conventional antimicrobial drugs. In particular, maluses of antimicrobial agents including inadequate dose and duration of treatment, long-term use as well as increasing environmental pollution are the major reasons (Sánchez-López et al. 2020). Moreover, an increasing number of deaths due to the infection of antibiotic-resistant pathogens are being reported almost every corner of the globe. Reports on new classes of resistance mechanism in life-threatening infectious pathogens, viz. *Mycobacterium tuberculosis*, *Helicobacter pylori*, *Vibrio cholerae*, *Entamoeba histolytica*, *Plasmodium falciparum* and many others, are continuously threatening mankind.

In this alarming situation, the exploration of noble metal nanoparticles has eventually come out as a boon for all. Bioactive nanoparticle itself or in combination with any antimicrobial drug can provide better intervention, especially against the drug-resistant pathogens (Dey et al. 2016; Chowdhury et al. 2018, 2020). Amongst the metal nanoparticles, silver (Ag), gold (Au) and platinum (Pt) are majorly explored for synthesizing therapeutic nanoparticles. These metal nanoparticles possess excellent antimicrobial activity and good penetration efficacy and exert a little or no toxic side effects on nontargeted cells and tissues (Dey et al. 2016; Chowdhury et al. 2018, 2020; Aziz et al. 2019; Inamuddin et al. 2021).

Another interesting feature in designing bioactive nanoparticles is appropriate surface modification. These metal nanoparticles (mainly Ag, Au) are usually functionalized with a variety of functional groups, such as polysaccharides, peptides, antibodies, RNA and DNA to promote their biomedical applications (Lee et al. 2020). Surface modification on metal nanoparticles provides several significant advantages. First, the modification provides an opportunity to stabilize nanoparticles against agglomeration. Second, it helps empower their self-organization, and, third, it creates interest to offer compatibility with others (Viswanathan et al. 2019). The clinical advantages achieved after surface modification are mentioned as good antimicrobial effect, high bioactivity, good cell growth and increased fatigue power (Izman et al. 2012). The organic ligands such as polysaccharides, peptides, amino acids, proteins, etc. are also considered as one of the good methods of surface modification to achieve the better outcomes. The organic groups are adequate to keep nanoparticles against accumulation; functional groups on nanoparticles surface may permit careful interaction of molecules with metal nanoparticles. The detailed working mechanisms of all these methods are explained previously in literature by many research groups such as Kango et al. (2013), Roy et al. (2014), Asri et al.
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(2017), Chowdhury et al. (2018), Qi et al. (2017), Mozetič (2019), Oun et al. (2020) and Liu et al. (2020). Hitherto, surface-modified AgNPs and AuNPs have been successfully explored as efficient antimicrobial and anticancer agents, drug and gene delivery vehicles, radiotherapy enhancement agents, important component in diagnostic assays and imaging, and many other healthcare sectors (Zhang et al. 2016; Lee and Jun 2019; Prasad et al. 2016; Aziz et al. 2019). The surface properties of newly synthesized nanoparticles remain insufficient many times in terms of low biocompatibility, toxicity and weak adhesion properties. Therefore, proper fabrication approach and selection of appropriate surface-modifying/surface-capping agent is considered as key prior to aim any kind of practical applications.

There are many reported metallic (noble and non-noble) and nonmetallic antimicrobial agents available, but many of them are found toxic to most of the living organisms. Therefore, to overcome this problem, different inorganic and metal-based antibacterial agents with sustainability, enhanced stability and biocompatibility are synthesized under strict processing conditions (Rajawat and Qureshi 2012; Hossain et al. 2015; Vijayakumari et al. 2019). Currently, Ag and Au are the major metallic-based nanoparticles utilized as antibacterial agents because of their long-term stability and excellent biocompatibility. Studies have proved that metal-based nanoparticles show biocidal activity against Gram-negative and Gram-positive bacteria (Roy et al. 2014; Franci et al. 2015; Chiriac et al. 2016; Rajeshkumar et al. 2016; Wang et al. 2017; Ovais et al. 2019; Chowdhury et al. 2020). The antimicrobial effects of metal nanoparticles have been attributed to their nano-size and high surface-area-to-volume ratio, which permits them to penetrate the bacterial membranes (Prasad and Swamy 2013; Aziz et al. 2014, 2015, 2016). The mechanisms of antibacterial effect of metallic nanoparticles are metal ion release, oxidative stress and non-oxidative-based stress existing instantaneously. These nanoparticles can serve only when nanoparticles interact with microbe’s cell walls; several approaches for the contact of microbes with the nanoparticles were used such as van der Waals forces, electrostatic attraction, receptor/ligand and hydrophobic interactions. After successful contact, metallic nanoparticles can pass through inner membranes, interact with metabolic paths and induce variations in membrane morphology. Once nanoparticles interact with microbes inside cellular machinery, it acts to prevent enzyme functions, disable proteins and electrolyte imbalance, induce oxidative stress and change gene expression scale (Vijayakumari et al. 2019). However, excessive quantity of microbes produces barrier that resists antimicrobial mediators and microbes avoiding the resistant system by forming superantigens. The extracellular polymeric secretion also produces everlasting attachment of microbes. In this chapter, we have presented a comprehensive overview on the therapeutic efficacy of noble metal nanoparticles against pathogenic microbes with a special emphasis on the mechanistic insights of their action at the biochemical, cellular and molecular level.
7.2 Chemistry of Noble Metal Nanoparticles

7.2.1 Design, Synthesis and Characterization

The work efficiency of noble metal nanoparticles mostly depends on the size of the nanoparticle and the stabilizing or capping or surface-modifying agents associated with it. The surface-modified nanomaterials should have biocompatibility to be useful for clinical purpose because without biocompatibility it cannot access the living cells. In addition to that, the synthesis procedure should be green in keeping the concern regarding environment in mind. There are two procedures for the synthesis of nanomaterial, i.e., top-down and bottom-up. Top-down is the scaling down of bulk material to the nano one by some mechanical process, and the bottom-up approach follows the reverse path. The process used in laboratories is the bottom-up approach. In this process, suitable bulk material containing the noble metal is reduced by a reducing agent and then scaled up to the nano one. A suitable capping agent is required here (Fig. 7.1). The efficiency of the capping material is very much important as it determines the size of the nanoparticles by stopping agglomeration to bulk. Chowdhury et al. (2018) presented the change in size distribution of AuNPs by using different polymeric (e.g., chitosan) and non-polymeric (e.g., tyrosine) substances as capping agents. The reduction procedure converting Ag⁺ to Ag⁰ also involves some amount of heat. Depending on the medium, reducing and capping

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**Fig. 7.1** Biosynthesis of noble metal nanoparticles, surface modification and its applications
agent, requirement of heat varies. Roy et al. (2014) showed the varying yield of nanoparticles depending on the source of heat.

Various inorganic and organic reducing and capping or surface-modifying agents are available globally. Some commonly used reducing agent are sodium borohydride, β-D-glucose, starch, negatively charged heparin, saccharides, polyoxometalates, bamboo hemicelluloses, sodium citrate, ascorbic acid, potassium bitartrate, maltose, etc. On the other side, surface-modifying agents are organic thiol compounds, surfactants, long-chain amine, carboxylates, starch, gum Arabic, gelatin, carboxymethyl cellulose, hydrogels, etc. (Roy et al. 2014; Dey et al. 2015, 2016).

But keeping the environmental concern in mind, the protocol for synthesizing surface-modified noble metal nanoparticles should be so designed that the solution medium, reducing agent and heating procedure, remains environment-friendly, i.e., green synthesis procedure should be adapted complying with 12 fundamental principles of green chemistry which focuses on minimization or total elimination of generated hazardous waste and maximization of the efficiency of chemical processes without compromising the safety concern of the products (Roy et al. 2014).

In recent times, studies conducted by Roy et al. (2014) and Chowdhury et al. (2018, 2020) showed that surface-modified AgNPs and AuNPs synthesized through green route are very much efficient in exerting lethal action on microbes including Gram-positive and Gram-negative bacteria, pathogenic fungus (Pichia guilliermondii) as well as parasite (microfilaria of Setaria cervi). Noble metal nanoparticles produced from the microbes have also been used for antimicrobial purpose against pathogenic organisms. For example, Ag nanoparticles synthesized from Bhargavaea indica, Brevibacterium frigoritolerans and Sporosarcina koreensis exhibited antimicrobial properties against Salmonella enterica, Vibrio parahaemolyticus, B. cereus, Bacillus anthracis and E. coli (Singh et al. 2016). Similarly, bowl-shaped AgNPs synthesized by Bacillus subtilis have been shown to possess excellent antibacterial, antifungal and antifilarial activities (Dey et al. 2016).

For characterization of nanomaterials, a lot of methods are available. The first-hand information about the formation of nanoparticles can be obtained from the signature peak UV-visible spectroscopy. To obtain the size and structure, transmission electron microscopy (TEM) is used. Scanning electron microscope (SEM) gives the information about the surface topology and shape of the material, while dynamic light scattering (DLS) gives the size distribution of the nanomaterial. The zeta potential study tells us about the stability of the nanoparticles. If the potential is more than +30V or less than −30V, then the nanoparticles is highly stable (Roy et al. 2014; Chowdhury et al. 2018, 2020). X-ray diffraction and Fourier transform infrared spectrometry are used to study the interaction between the nanoparticles and capping/surface-modifying agents. Spectrofluorometer is used to study luminescent nanoparticles. Herein, we have included a representative figure (Fig. 7.2) containing most of the commonly used characterization data for surface (chitosan)-modified AuNP (named as GC).
Fig. 7.2 Major characterization techniques for surface-modified noble metal nanoparticles. (A) UV-visible spectroscopic analysis. (B) TEM micrograph. (C) SEM study. (D) DLS study. (E) Zeta pot study
Since 1928, the discovery of antibiotics in medical science has brought an epoch, but the use of metals from the historic age has been helping us keep our body healthy. Metals have been found to be used as water disinfectant, food preserver, surgical wound healer as well as in treatment of leprosy, tuberculosis, gonorrhea and syphilis; metals have several satisfactory aspects (Lemire et al. 2013). Metals have numerous beneficial roles in maintaining our health but have limited use as antimicrobial therapeutics. Regarding the reports of drug resistance as well as lack of new antibiotics, researchers have found to turn their works towards metals to develop antimicrobials. There are several antimicrobial agents like ammonium compound, N-halamine siloxanes and heterocyclic compounds. However, these molecules possess low efficiency along with toxic effects on the living organism as well as environment, and most importantly nontargeted actions made those agents as out-listed (Shahid-ul-Islam et al. 2016). In this context, the use of nanoparticles of silver, gold and platinum are found to reflect potent antimicrobial activity along with low toxicity to human cells, long-term durability and improved biocompatibility. The effectiveness of these nanoparticles is accredited to its composition and surface properties (Ugru et al. 2018). In this section, we have discussed about different facets of nanoparticle-microbe interaction with a special emphasis on AgNPs and AuNPs.

### 7.3.1 Interaction of AgNPs with Pathogenic Microbes and Their Antimicrobial Effect

Beside various successful histories in textile, food storing and environmental programmes (Wijnhoven et al. 2009), AgNPs with its broad-spectrum antimicrobial activity against bacteria, virus, fungi and parasites prove their ‘oligodynamic property’ (Gaiser et al. 2009). One of the fascinating features of AgNP is its affinity and capacity of attachment with the microbial membrane/surface. AgNPs can be easily attached with the bacterial cell wall due to the presence of carboxyl, phosphate and amino groups (Abbaszadegan et al. 2015). In this regard, it has been evidenced that Gram-positive bacteria are less susceptible than that of Gram-negative (Malanovic and Lohner 2016). Phagocytosis and passive diffusion are the two main ways for the AgNPs to enter inside the bacterial cell (AshaRani et al. 2009; Carlson et al. 2008). In addition, it has been reported that AgNP also exploits the copper transport system (CTR) to enter the bacterial cell (Ghandour et al. 1988). The cytotoxic effects of the AgNPs are majorly imparted through the damage of membrane structure, leakage of cellular components (specially cytoplasm), DNA damage, inhibition of respiratory chain and collapsing protein motive force (Bragg and Rainnie 1974; Sondi and Salopek-Sondi 2004; Morones et al. 2005; Prasad et al. 2011, 2012; Swamy and Prasad 2012). Size is an important criterion in the bioactivity and biocompatibility of
AgNP. The study of Morones et al. (2005) revealed that AgNPs of 1–10 nm can efficiently bind to the surface of E. coli, V. cholera, S. typhus and P. aeruginosa and impart lethal action on these bacteria. Beside size, the shape of AgNPs is also known to play a crucial role in exerting microbicidal activity. Truncated triangular shape and sharp-edge triangular shape show better result over spherical and rod shaped (Pal et al. 2007; Dong et al. 2012). On the other hand, hydrogel-capped hexagonal and bowl-shaped AgNPs also have been documented for higher bioactivity against both Gram-positive and Gram-negative bacteria at a very low dose (Dey et al. 2015, 2016).

Interaction with cell membrane following induction of lipid peroxidation (LPO) is considered as a principal attribute in bioactive AgNPs. AgNP-induced LPO is usually diagnosed by estimating malondialdehyde, the end product of LPO (Chowdhury et al. 2020). Free radicals generated from LPO further enters into the chain reaction to generate more reactive oxygen species (ROS) that collectively induce oxidative stress leading to death of the microbial cells (Hwang et al. 2008; Kora and Arunachalam 2011; Saha et al. 2016). This postulation has been experimentally shown in AgNP-induced growth inhibition of E. coli (Hwang et al. 2008) and P. aeruginosa (Kora and Arunachalam 2011). Sulphur affinity is also an important characteristic of AgNPs which also facilitates its binding with the membrane proteins (Roy et al. 2019).

Beside antibacterial activities, AgNPs also found to inhibit viral growth using varieties of ways. PVP-coated AgNPs of 1–10 nm size have a potent antiviral effect in inducing interaction with envelope glycoprotein gp120 against HIV-1 (Lara et al. 2010a), while HSV-1 was found to be inhibited by MES (mercaptoethane sulfonate)-coated silver NPs (Baram-Pinto et al. 2009). Besides these, poxvirus, hepatitis B virus and influenza viruses were also found to be repressed by AgNPs (Rogers et al. 2008; Papp et al. 2010; Lu et al. 2008).

Several groups of protozoa have also been demonstrated as the targets for AgNPs. Plasmodium falciparum, the causative protozoan for malaria also found to be controlled by several silver nanoformulations with a significant efficacy in culture condition (Rai et al. 2017). In addition, surface-modified AgNPs are also capable of killing larvae of mosquitoes in terms of combat malaria (Saha et al. 2016).

Interestingly, AgNPs also interact with the various extracellular and cellular components of microfilaria (microscopic larval form of filarial parasites). In recent past, surface-modified green AgNPs have been found as extremely potent antifilarial agents. For example, AgNPs capped with chitosan, polyvinyl alcohol and hydrogel have been documented to interact with the cell membrane, induce ROS generation and lead to death of the microfilaria (Saha et al. 2014, 2016). In addition, lipid-coated AgNPs have been shown to possess anti-Wolbachian activity to reduce microfilarial growth (Ali et al. 2013). Wolbachia is an endosymbiotic bacterium that controls many important physiological functions of the filarial parasite (Mukherjee et al. 2018).

Nevertheless, AgNPs with exposed coating show a significant oligodynamic effect, but graphene oxide-silver NP composite (Ag-GO)-coated nanoplatform exert a more stronger effect as antimicrobial along with low side effects (Ghosh...
et al. 2019). The study of Wierzbicki et al. (2019) disclosed a higher effectivity of Ag-GO over *E. coli*, *S. aureus* and *Staphylococcus epidermidis* than AgNPs. GO sheets are decorated on AgNPs via thiol groups which provide effective results against both Gram-negative and Gram-positive bacteria. While chitosan-capped AgNPs were also found as both antibacterial and antifungal when treated against *E. coli* and *P. guilliermondii* (Roy et al. 2014), there are also several synergistic applications of AgNPs and antibiotics with satisfactory outcomes. Surface modification of AgNPs with amoxicillin (Kirthi et al. 2019), cephradine (Masri et al. 2018), streptomycin (Kora and Rastogi 2013), ampicillin (Tippayawat et al. 2017), vancomycin and amikacin (Kaur and Kumar 2019) has reflected better efficacy than separate use of antibiotics or AgNPs against bacterial pathogens, viz. *S. aureus*, *C. albicans*, *Acinetobacter baumannii*, *Enterococcus faecalis*, *Mycobacterium tuberculosis* and *E. coli*, respectively. Recently conjugation of AgNPs with various antibiotics and anthelmintics has been reported to provide better therapeutic efficiency (Dey et al. 2016). Therapeutic potential of AgNPs including their interactions with different microbes as well as their molecular targets have been presented in Table 7.1.

### 7.3.2 AuNP-Microbe Interaction and Antimicrobial Effect of AuNPs

The use of gold nanoparticles (AuNPs) are highly advantageous in diagnosis (e.g., microscopy) and treatment of human diseases including microbial infection due to its ability to scatter light in visible light regions and relative nontoxic nature (Khan et al. 2014). Besides that, potency to detoxify pollutants along with uses in formulation of biosensors and disease markers makes it more precious (Dykman and Khlebtsov 2011; Lopez et al. 2004). Antimicrobial activity of the gold complexes is a century-old discovery (Glišić and Djuran 2014). Various studies have pointed out that nanoparticles or formulation formed of gold produce different outcomes that depend on the characteristics of the formulation. First of all, the size that majorly influences the bioactivity (Brayner et al. 2006): the smaller one resembles greater toxicity than the larger one (Lin et al. 2013) and also achieves better permeation through the microbial membrane (Lopez-Chaves et al. 2018). A study by Ahmad et al. (2013) distinctly envisioned the differences between 7 nm and 15 nm AuNPs in inhibiting *Candida* sp., whereas other studies also found to indicate same story between 15 and 35 nm AuNPs (AshaRani et al. 2011; Chen et al. 2013a, b). Regarding the shape of AuNPs, diverse opinions have been reported in the context of the antimicrobial effects of AuNPs. Few studies have demonstrated spherical AuNPs as more toxic than rod-shaped, while non-spherical AuNPs have also demonstrated better toxicity (Liu et al. 2018). A study by Sultana et al. (2015) showed that the toxicity of flower-shaped AuNPs is more efficacious than the spherical ones. However, the toxicity of AuNPs not only depends on size and...
| Reducing agent                  | Surface modification | Size and shape            | Therapeutic applications                                                                 | References               |
|--------------------------------|---------------------|---------------------------|-----------------------------------------------------------------------------------------|--------------------------|
| Peel extract of *Carica papaya*| –                   | 10–35 nm and spherical    | Against Gram-negative bacteria: *Escherichia coli* and *Klebsiella pneumonia*          | Kokila et al. (2016)    |
|                                |                     |                           | Against Gram-positive bacteria: *Staphylococcus aureus* and *Bacillus subtilis*         |                          |
| Tuber extract of *Curcuma longa*| –                   | 18 ± 0.56 nm and spherical| Against Gram-negative bacteria: *E. coli* O157:H7                                     | Alsamarraie et al. (2018)|
|                                |                     |                           | Against Gram-positive bacteria: *Listeria monocytogenes*                               |                          |
| Fruit extract of *Tamarind indica*| –                   | 10 nm and spherical       | Against Gram-negative bacteria: *K. pneumonia*, *Salmonella typhi*, *E. coli* and *Pseudomonas aeruginosa* | Jayaprakash et al. (2017)|
|                                |                     |                           | Against Gram-positive bacteria: *B. subtilis*, *S. aureus*, *Micrococcus luteus* and *Bacillus cereus* |                          |
| Fruit extract of *Carambola sp.*| –                   | 10–40 nm and spherical    | Against Gram-negative bacteria: *E. coli* and *P. aeruginosa*                         | Gavade et al. (2015)    |
| Leaf extract of *Azadirachta indica*| –                   | 5–20 nm, spherical        | Against Gram-negative bacteria: *E. coli*                                             | Ahmed et al. (2016a)    |
|                                |                     |                           | Against Gram-positive bacteria: *S. aureus*                                           |                          |
| Leaf extract of *Ocimum sanctum*| –                   | 12–16 nm and spherical    | Against Gram-negative bacteria                                                          | Jain and Mehata (2017)  |
| Leaf extract of *Eriobotrya japonica*| –                   | 20 nm and spherical        | Against Gram-negative bacteria: *E. coli*                                             | Rao and Tang (2017)     |
|                                |                     |                           | Against Gram-positive bacteria: *S. aureus*                                           |                          |
| Leaf extract of *Lantana camara*| –                   | 410–450 nm and spherical  | Against Gram-negative bacteria: *E. coli* and *P. aeruginosa*                        | Shrinivas and Subhash (2017)|
|                                |                     |                           | Against Gram-positive bacteria: *S. aureus*                                           |                          |
| Extract of *Caulerpa racemosa* marine algae| –                   | 5–25 nm, spherical and triangular| Against Gram-negative bacteria: *Proteus mirabilis*                                  | Kathiraven et al. (2015)|
|                                |                     |                           | Against Gram-positive bacteria: *S. aureus*                                           |                          |
| Fungal biomass of Penicillium polonicum (ARA 10) | Neethu et al. (2018) | 10–15 nm, spherical and oval | Against Gram-negative bacteria: Salmonella enterica serovar Typhimurium, P. aeruginosa and K. pneumoniae, and Staphylococcus epidermidis | Against Gram-positive bacteria: S. aureus and P. breviscompactum |
| Fungal biomass of Phanerochaete chrysosporium (MTCC-787) | Saravanan et al. (2018) | 34–90 nm, spherical and oval | Against Gram-negative bacteria: E. coli, and P. aeruginosa | Against Gram-positive bacteria: S. aureus and S. epidermidis |
| Fungal biomass of Trichoderma longibrachiatum | Elmasi et al. (2018) | Variable size and spherical | Against Gram-negative bacteria: E. coli, and Acinetobacter baumannii | Against Gram-positive bacteria: S. aureus |
| Mycelial cell filtrate of Aspergillus brasiliensis | Omran et al. (2018) | 6–21 nm and spherical | Against Gram-negative bacteria: E. coli, and P. aeruginosa | Against Gram-positive bacteria: S. aureus |
| Cell-free supernatant of Pseudomonas aeruginosa (ATCC27853) | Quinteros et al. (2016) | 6–21 nm and spherical | Against Gram-negative bacteria: E. coli, and P. aeruginosa | Against Gram-positive bacteria: S. aureus |
| Mycelial cell filtrate of Trichoderma atroviride (KNIP001) | Kumar et al. (2018) | 25–45 nm and spherical | Against Gram-negative bacteria: E. coli, and P. aeruginosa | Against Gram-positive bacteria: S. aureus |
| Tyrosine Chitosan capped | Roy et al. (2014) | 13–22 nm and spherical | Against Gram-negative bacteria: E. coli, and P. aeruginosa | Against fungi: Pichia guilliermondii, and Microthrix of Setaria cervi |
| Tyrosine Polyvinyl alcohol capped | Saha et al. (2014) | 13–15 nm | Against Gram-negative bacteria: E. coli, and P. aeruginosa | Against fungi: C. albicans |
| Sodium 2-mercaptoethanesulfonate (MES)-capped | Baram-Pinto et al. (2009) | 4 nm | Against Human immunodeficiency virus type 1 (HIV-1) | Against Human immunodeficiency virus type 1 (HIV-1) |
| poly-N-vinyl-2-pyrrolidone (PVP) capped | Lara et al. (2010a) | 1–10 nm | – | – |
| Reducing agent | Surface modification | Size and shape | Therapeutic applications | References |
|----------------|----------------------|----------------|--------------------------|------------|
| –              | DNA-hydrogel capped and SHGel capped | 20 nm and bowl shaped | Against Gram-negative bacteria, *E. coli* Against Gram-positive bacteria, *B. subtilis* Against fungi *P. guilliermondii* Against microfilaria of *S. cervi* | Dey et al. (2016) |
| –              | GOSHGel capped       | 5 nm           | Against Gram-negative bacteria, *E. coli* Against Gram-positive bacteria, *B. subtilis* Against fungi *P. guilliermondii* | Ghosh et al. (2019) |
| –              | Ag-GO composite coated | Spherical      | Against Gram-negative bacteria, *Salmonella enteritidis* | Wierzbicki et al. (2019) |
| Sodium borohydride (NaBH₄) | Citrate, SDS and PVP capped | 21–70 nm and spherical | Increase activity of streptomycin, ampicillin and tetracycline in killing bacteria | Kora and Rastogi (2013) |
| Sodium borohydride (NaBH₄) | Cephradine-conjugated silver nanoparticles (Ceph-AgNPs) and vildagliptin-conjugated silver nanoparticles (Vgt-AgNPs) | 30–80 nm and spherical | Against Gram-negative bacteria, *E. coli* K1, *P. aeruginosa*, *K. pneumonia* | Masri et al. (2018) |
| Sodium borohydride (NaBH₄) | PVP, vancomycin and amikacin capped | 5–35 nm and spherical | Against Gram-negative bacteria, *E. coli* Against Gram-positive bacteria, *S. aureus* | Kaur and Kumar 2019 |
| Ethylene glycol | PVP coated           | 25 ± 4 nm and spherical | Against Gram-negative bacteria, *E. coli* Against Gram positive bacteria, *S. aureus* | Wang et al. (2016) |
| D-Maltose      | D-Maltose coated     | 86.81 ± 13.39 nm | Against Gram-negative bacteria, *E. coli* Against Gram-positive bacteria, *S. aureus* | Tippayawat et al. (2017) |
| Sodium hydroxide | Amoxicillin coated   | 35.50 nm, spherical and oval | Against Gram-negative bacteria, *E. coli* | Kirthi et al. (2019) |
shape but also on the surface chemistry, especially coating types and properties of the particles. According to Freese et al. (2012), AuNP coated with ethanediamine showed a better result in internalization of the particles inside the target cells. AuNP conjugated with different drugs have found to confer better delivery and treatment outcome. For example, AuNP-kanamycin complex applied against *S. epidermidis* and *Enterobacter aerogenes* revealed a very significant efficacy (Payne et al. 2016).

On the other side, improved efficiency of levofloxacin against *S. aureus*, *P. aeruginosa* and *E. coli* has been reported after conjugating with AuNPs (Bagga et al. 2017). Similarly, gallic acid-AuNP conjugate has been found effective against pathogenic bacteria like *Shigella flexneri* and *Plesiomonas shigelloides* (Rattanata et al. 2016). AuNPs of 4 nm size with sodium 2-mercaptoethanesulfonate (MES) was reported to be lethal against virus HSV-1 (Baram-Pinto et al. 2010), while AuNPs coated with amphiphilic sulphate-ended ligand can inhibit growth of HIV-1 (Di Gianvincenzo et al. 2010).

AuNPs are also effective against protozoan and helminth parasites. In this connection, antileishmanial activity of AuNP with 30 nm size found to cause around 75% inhibition of the parasite count which indicates towards the potency of this nanoformulation in pharmaceutical industries (Ahmad et al. 2016). AuNPs in single or in conjugated with indolicidin (a short 13-residue antimicrobial and cytolytic peptide) have several successful applications against fungal growth (Ahmad et al. 2013; Rahimi et al. 2019). Alike AgNPs, surface modification also plays a critical role in regulating the bioactivities and biocompatibility of AuNPs. Recent studies by Chowdhury et al. (2018, 2020) revealed chitosan-coated AuNPs as excellent antimicrobial agent displaying lethal effects on bacteria, fungus and microfilaria at a relatively lower dose than that of uncapped AuNPs. Moreover, surface modification with chitosan also found to enhance the stability and biocompatibility of the AuNPs (Chowdhury et al. 2018, 2020).

AuNPs have been found to execute better performance in delivering drug with hampering the physiological homeostasis. CHrPfs25 (codon-harmonized recombinant Pfs25, a *Plasmodium falciparum* protein used as vaccine antigen) when delivered in conjugation with AuNPs induces the expression of malaria transmission-blocking antibodies (Kumar et al. 2015). As a delivery vehicle, AuNP is not only restricted within the delivery of drugs, but also it has been found suitable to deliver proteins, genes and vaccines (Kong et al. 2017). In order to develop antimicrobial activity, internalization, i.e., cellular uptake of the AuNPs, is the primary criterion, and it is usually achieved by the attachment to the cell surface following clathrin-mediated endocytosis, non-specific endocytosis and phagocytosis (Mironava et al. 2010). Interaction of AuNPs with microbial cell membrane resulting in distortion of the membrane architecture (Huo et al. 2016; Rattanata et al. 2016) that finally leads to leakage of the cellular components (Payne et al. 2016). Inhibition of microbial growth also found to be mediated by blocking the H⁺-ATPase proton pumping (Wani et al. 2013) along with enhancing yield of ROS (Roy et al. 2018; Chowdhury et al. 2018). The study of Ahmad et al. (2015) showed how AuNP helps in elevating the number of ROS and in due time destroying cellular components to finally kill *Leishmania*. Moreover, AuNPs also can destroy transmembrane
| Reducing agent                        | Surface modification | Size and shape                  | Therapeutic applications                                                                 | References                        |
|--------------------------------------|----------------------|---------------------------------|------------------------------------------------------------------------------------------|-----------------------------------|
| Fruit extract of *Punica granatum*   | –                    | 5–17 nm, spherical and triangular | Against Gram-negative bacteria like *Salmonella typhi*, *Vibrio cholerae* and *Pseudomonas aeruginosa*  
Against Gram-positive bacteria, *Staphylococcus aureus*  
Against fungi *Aspergillus flavus* and *Candida albicans* | Lokina et al. (2014) |
| Fruit extract of *Solanum lycopersicum* | –                   | 14 nm, diverse                  | Against Gram-negative bacteria, *P. aeruginosa*  
Against Gram-positive bacteria, *S. aureus* | Bindhu and Umadevi (2014) |
| Nuts extract of *Areca catechu*      | –                    | 13.7 nm and spherical           | Against Gram-negative bacteria, *Escherichia coli*, *Klebsiella pneumonia*, *Enterobacter* and *P. aeruginosa*  
Against Gram-positive bacteria, *S. aureus* | Rajan et al. (2015) |
| Flowers of *Plumeria alba*            | –                    | 28 ± 5.6–15.6 ± 3.4 and spherical | Against Gram-negative bacteria, *E. coli* | Mata et al. (2016) |
| Root extract of *Trianthema decandra* | –                    | 33–99 nm and triangular         | Against Gram-negative bacteria, *E. coli*, *Proteus vulgaris*, *Yersinia enterocolitica* and *P. aeruginosa*  
Against Gram-positive bacteria, *B. subtilis*  
Against fungi, *C. albicans* | Geethalakshmi and Sarada (2013) |
| Root extract of *Mammea suriga*       | –                    | 22–50 nm and square             | Against Gram-negative bacteria, *E. coli* and *P. aeruginosa*  
Against Gram-positive bacteria, *B. subtilis* and *S. aureus* | Poojary et al. (2016) |
| Leaf extract of *Euphorbia hirta* L.  | –                    | 6–71 nm and spherical           | Against Gram-negative bacteria, *E. coli*, *K. pneumonia* and *P. aeruginosa* | Annamalai et al. (2013) |
| Leaf extract of *Solanum nigrum*      | –                    | 32 ± 6 nm and spherical         | Against Gram-negative bacteria, *E. coli* and *P. aeruginosa* | Muthuvel et al. (2014) |
| Source of Nanoparticles | Particle Size/Shape | Antimicrobial Activity | Reference |
|-------------------------|---------------------|------------------------|------------|
| Shell extract of *Chenopodium formosanum* | 8 ± 6 nm and spherical | Against Gram-negative bacteria, *E. coli* and *Staphylococcus saprophyticus* | Chen et al. (2019) |
| Aerial parts of *Rivea hypocrateriformis* | 10–50 nm and spherical | Against Gram-negative bacteria, *E. coli*, *P. aeruginosa*, and *K. pneumonia*; Against Gram-positive bacteria, *S. aureus* and *B. subtilis* | Godipurge et al. (2016) |
| Rhizome extract of *Acorus calamus* | Lesser than 100 nm and spherical | Against Gram-negative bacteria, *E. coli* and *S. aureus* | Ganesan and Gurumallesh Prabu (2019) |
| Stem extract of *Hibiscus cannabinus* | 13 nm and spherical | Against Gram-negative bacteria, *P. aeruginosa* and *S. aureus* | Bindhu et al. (2014) |
| Stem extract of *Maytenus royleanus* | 30 nm and hexagonal | Against parasite *Leishmania* sp. | Ahmad et al. (2015) |
| Sclerotial extract of *Lignosus rhinocerotis* | 10–25 nm, variable shape | Against Gram-negative bacteria, *P. aeruginosa* and *S. aureus* | Katas et al. (2019) |
| Sodium citrate | Kanamycin capped | 20 ± 5 nm and spherical | Payne et al. (2016) |
| – | Bromelain capped and levofoxacin conjugated | 38.11 ± 2 nm | Bagga et al. (2016) |
| – | Human serum albumin and levofoxacin conjugated | 27.2 ± 1 nm | Bagga et al. (2017) |
| – | Indolicidin conjugated | 30 nm and spherical | Rahimi et al. (2019) |
| Reducing agent | Surface modification | Size and shape | Therapeutic applications | References |
|----------------|----------------------|----------------|--------------------------|------------|
| Sodium borohydride (NaBH₄) | Sulphate-ended ligand coated | variable | Against human immunodeficiency virus (HIV) | Di Gianvincenzo et al. (2010) |
| Sodium borohydride (NaBH₄) | Amoxicillin coated | 79 ± 43 nm | Against Gram-positive bacteria, *S. aureus* | Silvero et al. (2018) |
| – | Sodium 2-mercaptoethanesulfonate (MES) capped | 4 nm | Against *Herpes simplex virus type 1* (HSV-1) | Baram-Pinto et al. (2010) |
| – | Galic acid conjugated | 17 nm | Against Gram-negative bacteria, *Shigella flexneri* and *Plesiomonas shigelloides* | Ratanata et al. (2016) |
| Essential oil of *Nigella sativa* (NsEO) | NsEO coated | 15.6 to 28.4 nm and spherical | Against Gram-positive bacteria, *S. aureus* | Manju et al. (2016) |
| Dextran | Dextran coated | 22 ± 3 nm | Against Gram-negative bacteria, *E. coli* | Nath et al. (2008) |
| *Piper nigrum* extract | Chitosan capped | 1–10 nm | Against microfilaria of *Setaria cervi* | Saha et al. (2017) |
| *Terminalia chebula* extract | Chitosan capped | 10 nm | Against microfilaria of *Wuchereria bancrofti* and *S. cervi* | Roy et al. (2018) |
| Chitosan | Chitosan functionalized | 10–50 nm | Against microfilaria of *S. cervi* | Chowdhury et al. (2018) |
electrostatic efflux (Li et al. 2010) to execute their antimicrobial activities. Herein, Table 7.2 describes the composition and antimicrobial effects of the AuNPs available till date.

7.3.3 Antimicrobial Effect of PtNPs

The novel nano-tool PtNP is now in top of interest. Platinum is now being used extensively in automotive and chemical industries to develop catalytic convertor and new chemical compounds (Shi et al. 2015). For instance, platinum is also found to use in generating eco-friendly energy sources (Madsen et al. 2011). Beside of all these, several reports have also highlighted that platinum is also beneficial for pharmaceutical industries as platinum has activity in producing bio-imaging, detecting biological molecules and modulating nanomedicine (Tanaka et al. 2011; Moglianianni et al. 2016; Rao et al. 2016). Several physical and physio-chemical properties like, size, shape, surface structure and capping agent along with the dispersion state and stability help optimize and finally lead to formulate the desired PtNPs with specific target-based activity. However antibacterial activity of the platinum first came in public in 1965 (Pedone et al. 2017), but antimicrobial activity of the nanostructured platinum has not been explored yet. PVP-conjugated PtNPs with 1 to 3 nm size have been reported as effective against the bacterium, *P. aeruginosa* (Gopal et al. 2013). In another study, pectin-capped PtNPs showed an efficacy against both Gram-positive and Gram-negative bacteria (Pedone et al. 2017). Green synthesis of PtNPs using *Garcinia mangostana* fruit extract also found as successful in inhibiting the growth of various bacteria like *P. aeruginosa, K. pneumonia, B. subtilis* and *S. aureus* (Nishanthi et al. 2019). There are limited number of reports published yet, but effective radical-scavenging property will make PtNP as the most success nanomedicine in the upcoming future. However, the use of PtNP as biomedicine is still in contradictory stage. Antimicrobial activities of PtNPs alongside their interactions of with different microbes based on the available reports are listed in Table 7.3.

7.4 Intracellular and Intercellular Targeted Delivery of Nanoparticles

The intracellular and intercellular delivery of nanoparticles is the most important aspect in the development of therapeutic nanoparticles for various applications like its use as antimicrobial and immunomodulatory drugs, anticancer agents, cellular modulators and nanodevices for studying cell organelles (Paulo et al. 2011; Prasad et al. 2017). The development of smart noble nanoparticles requires appropriate surface modifications which facilitate the use of the nanoparticles directly as
Table 7.3 Therapeutic applications of PtNPs as an antimicrobial agent

| Reducing agent                              | Surface modification | Size and shape                      | Therapeutic applications                                                                 | References          |
|---------------------------------------------|----------------------|-------------------------------------|------------------------------------------------------------------------------------------|---------------------|
| Polyaniline and Ag-Pt bimetallic colloidal | --                   | 2–3 nm                              | Against Gram-positive bacteria: *S. aureus* and *Streptococcus* sp.                        | Boomi et al. (2013) |
| Extract of seaweed *Padina gymnospora*      | --                   | 25 nm, truncated, octahedral, tetrahe- | Against Gram-negative bacteria: *Escherichia coli*, *Salmonella typhi* and *Klebsiella pneumonia*  | Ramkumar et al. (2017) |
|                                             |                      | dral and spherical                   | Against Gram-positive bacteria: *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Lactococcus lactis* and *Streptococcus* mutants |                     |
| Fruit extract of *Garcinia mangostana*      | --                   | 20–25 nm and spherical               | Against Gram-negative bacteria: *P. aeruginosa* and *K. pneumonia*                        | Nishanthi et al. (2019) |
|                                             |                      |                                     | Against Gram-positive bacteria: *B. subtilis* and *S. aureus*                            |                     |
| Hexachloroplatinate and apigenin            | --                   | 1–2 nm and spherical                 | Against Gram-negative bacteria: *P. aeruginosa*                                          | Gurunathan et al. (2019) |
| Sodium hydroxide                            | PVP                  | 1–3 nm, sphere, cuboids and flower shaped | Against Gram-negative bacteria: *P. aeruginosa*                                         | Gopal et al. (2013) |
| Sodium borohydride (NaBH₄)                  | Pectin capped        | 2–5 nm                              | Against Gram-negative bacteria: *Escherichia coli* and *P. aeruginosa*                    | Ahmed et al. (2016b) |
|                                             |                      |                                     | Against Gram-positive bacteria: *B. subtilis* and *S. aureus*                            |                     |
| Plant extract of *Taraxacum laevigatum*     | Phytochemicals capped | 2–7 nm, spherical                   | Against Gram-negative bacteria: *Pseudomonas aeruginosa*                                 | Tahir et al. (2017) |

(continued)
therapeutics and/or cargo for the drugs (Karimi et al. 2016). In order to deliver the therapeutics to different intracellular cellular targets, internalization of AgNPs/AuNPs involves binding with the membrane receptors leading to receptor-mediated endocytosis (Panzarini et al. 2018). In addition, indirect incorporation through hydrophobic and electrostatic interaction with phospholipid bilayer has also been reported (Chou et al. 2011). Upon entering the cytoplasm, the mobility of the ingested nanoparticles depends on the size and biological interactions with the various organic and inorganic constituents of cytoplasm and targeted organelles. In this context, peptide conjugation with the nanoparticles enhances its distribution across the cell by recognizing the nuclear localization signal (NLS), mitochondrial localization signal and trafficking to endoplasmic reticulum (ER) (Paulo et al. 2011).

Taking clue from AgNPs and AuNPs, superparamagnetic iron oxide NPs (SPIONs) are nowadays used along with the mitochondrial targeting peptide (MTP) to differentiate the intracellular proteins and play an important function in regulating the cellular trafficking across the endocytotic pathway, localization of the protein within the plasma membrane and for the cellular uptake of basic amino acids (Salaklang et al. 2008).

In recent times, AuNPs, AgNPs and silica nanoparticles have been utilized/attempted for targeting various biomarkers associated with cancer, autoimmune and infectious microbial and parasitic diseases. Owing to its surface properties and affinity towards cell surface molecules (as discussed in the earlier section), AgNPs can easily cross the cell membrane and can deliver a drug of choice. However, this

| Reducing agent | Surface modification | Size and shape | Therapeutic applications | References |
|---------------|---------------------|--------------|-------------------------|------------|
| Sodium borohydride (NaBH₄) | Jacalin capped | 3.1 ± 1.6 nm | Against Gram-negative bacteria: *Aeromonas hydrophila* | Ahmed et al. (2018) |
| Sodium hydroxide | Curcumin stabilized | 3.8 nm | Against Gram-negative bacteria: *E. coli* Against Gram-positive bacteria: *S. aureus* | Yu et al. (2019) |
| Doxycycline | Doxycycline capped | 10–20 nm | Against Gram-negative bacteria: *E. coli, Salmonella typhimurium* Against Gram-positive bacteria: *Streptococcus pyogenes* and *S. aureus* | Safdar et al. (2020) |
phenomenon is dependent on the size of the AgNPs. Previously, Dey et al. (2016) demonstrated the uptake of hydrogel-capped AgNPs inside by mouse macrophages, and the presence of AgNPs within the cell was confirmed by HR-TEM following EDX. These AgNPs were also reported to load streptomycin, diethylcarbamazine and albendazole (Dey et al. 2016). On the other side, nontoxic nature of AuNPs enables smooth delivery of drugs which can control the protein expression within the cell and used as an intracellular sensor in many diseases (Rosi et al. 2006). AuNPs formed by poly(γ-glutamic acid) conjugated with L-phenylalanine (40–200 nm) are assigned for the protein delivery through absorption and release within the cytoplasm and can be used as an agent for the vaccine development and signalling pathway modulators (Akagi et al. 2011). The polymeric NPs consist of the self-assembly structure and dendrimers loaded with hydrophilic and hydrophobic drugs and conjugated to targeting moieties to serve as an active cellular target for human diseases, mainly cancer (Nag and Delehanty 2019). Thus, the application of both AgNPs and AuNPs for the intracellular and intercellular targeting for specific cellular and subcellular components enhances the potential of these nanomaterials as molecular fluorescent agents, detection probes and the therapeutic factors for drug development to counteract various human diseases.

Several developmental research and modifications are currently going on to improve the efficacy of the nanoparticles, especially the cell-penetrating property. Quantum dots (QDs) are the best examples of the modern version of nanotherapeutics. QDs are semiconductor crystals that are made up of the group II–VI, III–V or IV–VI atoms from the periodic table and perform an extensive function of size-tunable fluorescent emission and broad excitation spectra, leading to beneficial for single as well as multiple molecule tracking (Ruedas-Rama et al. 2012). The quantum dot coated with poly(ethylene glycol) (PEG) and NLS is microinjected showing active transport and accumulation across the nucleus and when coated with fluorescent protein shows association with cell line across the cytoplasm (Derfus et al. 2004; Medintz et al. 2008). The microinjection of phospholipid-coated quantum dots to the early embryo of *Xenopus* to monitor the physiological changes along the development leads to developmental abnormalities (Dubertret et al. 2002). The main characteristic features of liposomes include high biocompatibility, simple surface modifications and flexibility across switching between both hydrophobic and hydrophilic drugs. Liposomes can easily incorporate the functional phospholipids across various target moieties and increase its efficiency for cellular targeting and therapeutic efficacy (Gabizon et al. 2006; Nag and Delehanty 2019). Poly(lactic-co-glycolic acid) (PLGA) serves as both an intercellular and intracellular target and is being used for co-staining the actin and mitochondria using antibody-conjugated quantum dots and MitoTracker Red, respectively (Chou et al. 2011). It is distributed across the early endosomes, Golgi apparatus and endoplasmic reticulum based on the cellular internalization and types of cells to enhance the specificity of drug delivery and therapeutic development (Cartiera et al. 2009). In a recent report by Mondal et al. (2019), luminous benign QDs have been reported for excellent intracellular imaging and delivery of antimicrobial drug (streptomycin). These streptomycin-loaded QDs were found to cure
peritonitis in mice model, and the efficacy was higher than free streptomycin (Mondal et al. 2019). The various types of nanoparticles associated with the targeted delivery across the intracellular and intercellular components of cells are listed in Table 7.4.

| Types of nanoparticles | Mechanism of action and damage | References |
|------------------------|--------------------------------|------------|
| Silver NP              | Internalized via scavenger receptor-mediated phagocytosis, mitochondrial damage, induces apoptosis and cell death | Singh and Ramarao (2012) |
| Gold NP                | Passive delivery, controls protein expression in cell, nontoxic | Rosi et al. (2006) |
| Silica NP              | Inhibits kinase activity by delivering antibody against phospho-Akt intracellularly, translation inhibitors ribosome-inactivating proteins (RIPs) | Bale et al. (2010) |
| Quantum dot            | Microinjected quantum dot coated with florescent protein, phospholipid coat, penetrates peptide, vesicle fusion, reminiscent actin/kinesin-mediated active transport | Ruan et al. (2007) |
| Liposomes              | Targeting cancer cells, incorporate functional phospholipids and enhance cellular targeting | Patil et al. (2016) |
| PLGA                   | Dispersed across endosome, Golgi apparatus, ER, causes cell internalization, greater intracellular drug accumulation | Cartiera et al. (2009) |
| Superparamagnetic iron oxide NPs (SPIONs) | Mitochondrial targeting, regulate cellular trafficking, endocytotic pathway | Salaklang et al. (2008) |
| NPs formed by poly(γ-glutamic acid) conjugated with L-phenylalanine (40–200 nm) | Protein delivery: absorb protein and release in cytoplasm, targeted for vaccine development, signalling pathway interference | Akagi et al. (2011) |
| Polymeric NPs          | Active cellular targeting for cancer, loaded with hydrophilic and hydrophobic drugs and conjugated to targeting moieties | Nag and Delehanty (2019) |
| Poly(propyleneimine) (PPI) dendrimers | siRNA-mediated cancer cell targeting, accumulation of siRNA in the cytoplasm of cancer cells and gene silencing | Taratula et al. (2009) |
7.5 Cellular and Molecular Mechanism of Antimicrobial Action of Noble Nanoparticles

Considering the broad-spectrum antimicrobial activity of the noble metal nanoparticles, the mechanisms of action of different nanoparticles have been studied at cellular and molecular levels employing both in vitro and in vivo experimental setup. Till date a number of approaches have been exploited to synthesize noble metal nanoparticles, and intriguingly the surface-modified nanoparticles have been found to possess more efficient antimicrobial activity (Roy et al. 2014; Chowdhury et al. 2018; Prasad et al. 2020). Various studies conducted on exploring the antimicrobial activity of noble metal nanoparticles revealed AgNPs as more reactive than AuNPs, while AuNPs are more benign than that of the AgNPs (Roy et al. 2014; Chowdhury et al. 2018). Interestingly surface modification of AgNPs and AuNPs by polysaccharide (like chitosan) was found to improve the bioactivities of both nanoparticles (Roy et al. 2014; Chowdhury et al. 2018, 2020). Firstly, such enhancement in bioactivity is not solely contributed by the surface-modifying agent, rather the capping agent helps in the movement of the encapsulated nanoparticles in it the biological medium; secondly, it gets easily attached at the binding sites of the cell membrane of the targeted cell; and, thirdly, it remains attached for a long time favouring the release of the particles into the cell. All of these activities of the surface-modifying agent helping the targeted drug delivery in turn help the nanoparticles reach the requisite site and execute the task.

Once the size of particles approaches the nanoscale (1–100 nm), various a typical classical and quantum mechanical phenomena appear to be extant which are usually absent in matter beyond the upper and lower limits of this size range. This lays down the foundation of the antimicrobial properties of the noble nanoparticles. It is well observed that these physiochemical properties owe to and are regulated by their physical characteristics like size, shape, overall crystal structure, surface-area-to-mass ratio, as well as the ζ-potential at their slipping planes. However, mechanisms of action of the nanoparticles can be generalized under three varied models such as reactive oxygen species (ROS) induction, non-ROS mechanisms and metal ion release mechanisms as we have depicted in Fig. 7.3. However, it is to be well noted that a nanoparticle may function through one or more mechanisms simultaneously.

In general, noble metal nanoparticles first interact with the membrane of the target microbial cells. This interaction results in the induction of lipid peroxidation (LPO) of membrane lipids. LPO generates several free radicals that initiates chain reaction to generate more radicals by damaging the cellular biomacromolecules. In fact, free radical species have a very special property of generating furthermore free radicals by cleaving existing covalent bonds in the surrounding molecules, and the resulting free radicals produce more such species in a chain reaction fashion; this occurs at an exponential rate. It wreaks havoc in any biochemical system by disrupting the existing bonding interactions holding the system together, and this capacity is known as oxidative stress.
Additionally, quantitative real-time polymerase chain reaction (RT-PCR) studies show that ROS also increases the expression levels of a general stress response gene (Dna K) and two oxidative stress genes (Kat A and Ahp C) of oxidative proteins, which thereby causes extensive damage to the intracellular components (Gurunathan et al. 2012). ROS production can be induced by noble nanoparticles (Gurunathan et al. 2012) via different mechanisms—one such mechanism is illustrated in the photocatalytic model; it states that when nanoparticles absorb photons of energy equal to or greater than the band gap, their electrons get promoted to the conduction band from the valence band leaving behind a hole in the valence band—which are definite theoretical antivalents of the physical electrons and thus carry a positive charge and flow against the direction of electron movement. These holes are present on the surface of the metal oxides and when they react with the surrounding H₂O or (OH⁻) or O₂ species, they produce hydroxyl (OH⁻) and superoxide radicals (O₂⁻). Furthermore, it was also observed that ultrasonic activation is yet another mechanism for inducing ROS formation by which nanoparticles split the surrounding H₂O into H⁺ and can react with dissolved O₂ to generate H₂O₂. Studies show that the negatively charged superoxide and hydroxyl radicals are unable to penetrate the cell membrane and function while being attached to the cell surface; H₂O₂ on the other hand is able to penetrate the cell membrane and cause extensive cellular damage. As already mentioned, ROS axes are not the only mechanisms by which the antimicrobial properties of the nanoparticles are mediated. Observations against several studies using Fourier transform infrared (FTIR) analysis, electron spin resonance,
liquid chromatography-mass spectrometry, transmission electron microscopy (TEM), proteomics tools and flat cultivation show that various nanoparticles have efficient antimicrobial properties no matter if used under UV light, natural light or absolute darkness. Yet another antimicrobial mechanism of nanomaterial is attained by slow and sustained release of metal ions from metal nanocomposites, as in the case of AgNPs which are currently being used by embedding them on zeolite membranes (Tavolaro and Drioli 1999). In this mechanism the released metal ions are absorbed through the cell membrane, and once inside the cell, they are free to interact directly with functional groups of proteins and nucleic acids such as sulfanyl (–SH), amino (–NH) and carboxyl (–COOH) groups. This confers damage to the enzyme activity, the cytoskeletal structure and the overall physiological processes of the cell, ultimately inhibiting the organism as a whole.

The cells have natural mechanisms of producing such free radical species or free radical-generating species, called reactive oxygen species (ROS) which includes mainly four species like the superoxide anion (O₂⁻), the hydroxyl radical (OH•), the hydrogen peroxide molecule (H₂O₂) and the singlet oxygen species (¹O₂). They are quite capable of generating free radicals as described above, but they possess different levels of dynamics and activity. Under normal conditions, cells generate cytoplasmic ROS, but this alteration in cellular redox potential is balanced by the generation of antioxidant species which counters the exponential increase of ROS, keeping the species concentrations within redox equilibrium limits. This equilibrium is useful in maintaining regular cellular homeostasis and appears to play an important role in cellular signalling and disease pathophysiology. However, upsetting this equilibrium produces oxidative stress which results in a change in permeability and integrity of the cell membrane mostly by causing peroxidation of the membrane lipids (Cheloni et al. 2016); it also deals damage to nucleic acids and various proteins. NPs as filaricidal diminished the activities of enzymes SOD, catalase and GPx that are most vital in antioxidant defence mechanism (Jeeva et al. 2015). On the other side, GSH is a sulphur-containing protein that functions as antioxidant by carrying the reactive electrons from the peroxide and its level is usually depleted after filaricidal induction (Mukherjee et al. 2016). But, an inclined level of glutathione-S-transferase (GST) maintains a high ROS level in mitochondria, endoplasmic reticulum and peroxisome which is known to signal apoptosis (Mukherjee et al. 2016).

ROS-mediated apoptosis has a close relation with DNA damage, while noble nanoparticles also display DNA-binding property. Previous studies in this direction revealed that chitosan-capped and supramolecular hydrogel-capped AgNPs preferentially bind at the minor groove of bacterial as well as parasitic DNA (Roy et al. 2014; Dey et al. 2016). Therefore, AgNP-induced ROS and direct binding of AgNP to microbial DNA result in p53 activation that most likely signals activation of apoptotic pathways. In case of microfilaria, chitosan-/hydrogel-capped AgNPs activate cell death abnormal (CED) pathway, and caspase mediates pathways to cause cell death (Roy et al. 2014; Dey et al. 2016). Egg-laying defective (EGL)-1, CED-3, CED-4 and CED-9 are four essential proteins essential for CED pathway in microfilaria. During apoptosis CED-9 is negatively regulated by EGL-1 and fails to show
dominancy over CED-4 and CED-3 (Shaham and Horvitz 1996). In normal-living filarial cell, CED-4 dimers are sequestered with CED-9 on the outer surface of the mitochondria and inhibit apoptosis (Lettre and Hengartner 2006). In time, stimulation after an apoptotic induction increased the level of EGL-1 and makes bonding with CED-9 by BH3 domain that in turn disrupt CED-4–CED-9 complex (Yan et al. 2004, 2005). After dissociation of CED-9, two asymmetric CED-4 dimers oligomerize to make a tetrameric apoptosome, and this tetrameric structure then recruits proCED-3 molecules (Huang et al. 2013). Next to that, CED-3 (a cystine protease) becomes activated and executes apoptosis. A study by Mukherjee et al. (2016) revealed a rich level of cystine protease family protein, caspases, which direct a new path suitable for microfilarial apoptosis. Caspase proteins, viz. cas-9, cas-8 and cas-3, cytochrome c and poly (ADP-ribose) polymerase (PARP) are the main mediators that are responsible for intrinsic and extrinsic apoptosis. The generalized model of the mechanism of action of noble metal nanoparticles is demonstrated in Fig. 7.4.

### 7.6 Therapeutic Promises of Nanoparticles as Antimicrobial Agents, Prospects and Challenges

Nanotechnologies most specifically nanoparticles are now in good demand in pharmaceutical industries. This new therapeutic strategy can deliver drug most accurately and exert the desired function at a very low dose. As we all know, treatment of HIV needs antiretroviral drugs, ritonavir, lopinavir and efavirenz, but they have very low sustainability in physiological conditions. In this context, the use of nanoparticles formulated using poly(lactic-co-glycolic acid) (PLGA) can enhance the sustained release of the anti-HIV drugs from 48 h to 4 weeks (Rizvi and Saleh 2018). Similar kind of phenomena also found as evidence when poly(lactic-co-glycolic) (PLG) AgNPs encapsulated with rifampin, isoniazid and pyrazinamide drugs were used against tuberculosis. Detection of rifampicin for 4 days in blood and 9 days in tissues along with 9 to 11 days of retention for isoniazid and pyrazinamide in blood and tissue strongly indicates higher potency of nanoformulation over unbound drugs (Gelperina et al. 2005). Moreover, esculentin-1a-capsulated nanostructures are found as 17 times more effective than free esculentin-1a as anti-\textit{P. aeruginosa} therapeutic (Yeh et al. 2020). Another study on chitosan-coated AgNP-conjugated form with ciprofloxacin displayed a better MIC than the free drug against \textit{E. coli} (Kumar et al. 2016), while the encapsulated daptomycin form can enhance the release time up to 4 h (Silva et al. 2015). Besides that, phosphate- and polyphosphate-conjugated PEG nanoparticles also can sustain the release of phosphate to 100 h (Yin et al. 2017). According to the findings of Fan et al. (2019), polyethylene glycol-functionalized AuNP when applied in conjugation with ampicillin almost 18% lower MIC was found than ampicillin alone against \textit{S. aureus}. Several surface-modified nanoparticles have also been reported for affecting...
bacterial biofilm. PLGA/chitosan-coated nanoparticles when conjugated with colistin anti-*P. aeruginosa* biofilm effect found to last for 72 h that is much an improved report than free colistin (d’Angelo et al. 2015). Interestingly, 0.0156 μg/ml of

Fig. 7.4 Insights of ROS-mediated apoptosis induced by noble metal nanoparticles
ciprolfloxacin encapsulated with PLGA was found sufficient to eradicate \textit{P. aeruginosa} biofilm within 3 days only (Baelo et al. 2015).

Bacterial synthesis of nanoparticles is now considered as a new trend as bacteria are able to hydrolyse metal compounds and reduce metal ions to form nano in a green way. While the study of Prakash et al. (2011) showed the level of potentiality of AgNP synthesized by \textit{Bacillus cereus} in diminishing the growth of \textit{E. coli} and \textit{Streptococcus}. Another work summarized that only 5 μg/ml of concentrated AgNP of \textit{Bacillus} is sufficient to generate antimicrobial activity against \textit{E. coli}, \textit{Pseudomonas aeruginosa}, \textit{Proteus mirabilis}, \textit{Serratia marcescens} and \textit{Klebsiella} sp. (Yokesh Babu et al. 2013). A report by Dey et al. (2016) demonstrated a synthesis of flower-shaped novel AgNPs by \textit{B. subtilis}, and these AgNPs were found to be active even at a dose of 1.25 μg/ml against bacteria, fungus and parasite.

In biological methods of nanoparticles, formulation with bacteria is not only a single option, but the use of fungus also has several successes in works. A recent study on sclerotial extract of \textit{Lignosus rhinocerotis}-mediated synthesis of AuNPs explained very high antimicrobial activity against Gram-negative \textit{P. aeruginosa} and \textit{E. coli} and Gram-positive bacteria \textit{S. aureus} and \textit{Bacillus} sp. (Katas et al. 2019).

Nanoparticle exploitation is not only limited to bacterial, viral and fungal inhibition, but it is also in evidence that they have much potency in eradicating microparasites. The study of Saini et al. (2016) and Saha et al. (2017) found that AgNP as well as AuNP both have the ability to eliminate microfilariae of \textit{Setaria cervi}. Similarly, the study of Roy et al. (2018) showed the efficacy of \textit{Terminalia chebula} extract. AuNP fully depends on degradation of nuclear DNA. This data was further supported by the work of Yadav et al. (2020) that described AgNPs synthesized using \textit{Andrographis paniculata} leaf extract elevate the ROS level and generate oxidative stress that finally leads to filarial death via induction of apoptosis. In addition, Wolbachia depletion using polyanhydrated nanoparticle as delivery medium of doxycycline can also reduce microfilarial abundance at a very low dose. Besides these, it has also been reported that the use of transferrin-conjugated solid lipid-coated AgNPs is a more effective antimalarial than unconjugated form (Gupta et al. 2007), while a little improvement was documented when AgNPs were used with violacein as anti-plasmodium (Rahman et al. 2019).

All of the reports or findings described above are showing the improvement of therapeutics, and all the success is due to development of nanoformulation (Prasad et al. 2019). Effective and specific targeting, electrostatic interactions, stabilizing and reducing capabilities and drug delivery role along with toxic nature to microbes with low side effects to humans play a crucial role to achieve the therapeutic potentiality. Even the interaction property with intracellular components helps enhance the therapeutic ability and that finally differs it from other treatments. The DNA-binding ability of the nanoparticles creates a milestone in medicinal science. Polymer-stabilized and surface-modified (using chitosan, polyethylene glycol, polyvinyl alcohol and styrene) AgNPs can bind to \textit{E. coli} DNA molecule and disrupt that to inhibits bacteria replication (Roy et al. 2014). In support another study of Li et al. (2013) clearly visualized with AFM topography that AgNPs and citrate-modified
AuNPs are capable of binding to microbial DNA molecule to cease the DNA replication.

The use of nanoparticles is advantageous, but the synthesis procedure should follow biological eco-friendly as well as benign green synthesis approach rather than heftiest physical and chemical processes. Moreover, surface modification using modifying agents has an opportunistic effect to ameliorate toxicity of the nanoparticles. For example, chitosan-functionalized AgNPs/AuNPs suggest that the use of chitosan minimizes the cytotoxic level of the noble metal nanoparticle along with an increase of the bioactivity activity inducing ROS generation (Roy et al. 2014; Chowdhury et al. 2018, 2020). In addition, two interesting studies conducted by Dey et al. (2015, 2016) revealed capping of AgNPs using supramolecular hydrogel (SHGel) and DNA hydrogel increases the bioactivity and decreases the toxic effects. Other coating agents like PVP and citrate also have been reported to minimize the cytotoxicity of noble nanoparticles (Akter et al. 2017). All of these surface modifications also enable the drug-loading capacity of the noble nanoparticles of metal and improvement of the efficacy of loaded drug. The antimicrobial activity of amoxicillin, penicillin G, clindamycin, vancomycin and erythromycin was found to be improved owing to the conjugation of polymer-coated AgNPs (Rai et al. 2009). Though noble nanoparticles possess an excellent ability to inhibit microbial growth in vivo and in vitro, still there are some contradictions against their use as therapeutics regarding the side effects and bioavailability. In this connection, so modern approaches of nanotechnologies like tunable nanoparticles, quantum dots, nanogels, etc. are evolving rapidly to meet the current need.

Microbial diseases are the continuous threat to all living creatures from the prehistoric times. Discovery of antibiotics was a challenge to ride above those diseases. But accumulation of resistance against antibiotics has created a difficult situation nowadays. While in several experiments, the use of noble metal nanoparticles provides a hope that they can be effective over microbes. In addition, metal and metal oxide-formulated nanoparticles have been found as the potent killer of multidrug-resistant bacteria as well. The study of Franci et al. (2015) pointed the ability of AgNPs against methicillin-resistant S. aureus (MRSA) and methicillin-resistant S. epidermidis (MRSE), while efficacious report against ampicillin-resistant E. coli, multidrug-resistant Pseudomonas aeruginosa and erythromycin-resistant Streptococcus pyogenes highlighted AgNPs as a potent antibiofilm and antibacterial formulation (Lara et al. 2010b). In this regard AuNPs are also proved as highly active as several studies showed effectivity in inhibition of growth of multidrug-resistant bacterial strain of E. coli, S. aureus and Salmonella typhimurium (Bressee et al. 2011; Dasari et al. 2015). Despite these successes, more and more researches on developing new smart noble metal nanoparticles as well as new approaches for tuning the size and physico-biochemical properties of the nanoparticles also are in progress to counteract the emerging microbial disease.
In the mid-2020, the whole world is still under pressure of several microbial diseases. Antimicrobial drug development is therefore considered as one of the most practicable research works at present time. Even most of the pharma companies are investing to develop better therapeutic solutions against the life-threatening infectious diseases caused by *Mycobacterium tuberculosis*, *Helicobacter pylori*, *Vibrio cholerae*, *Entamoeba histolytica*, *Plasmodium falciparum*, and many others. These microbial pathogens are not only a curse for human health but also a result in huge economic losses by affecting the health of economically important animals like poultry, cattle and other livestock. Considering the urgency, several effective antibiotics have been developed to combat microbial diseases and are available in the market. However, emergence of resistance against these drugs due to the maluses has created an alarming situation. In this scenario, the use of bioactive noble metal nanoparticles has shown better therapeutic efficiency in terms of low treatment dose, less toxicity and absence of microbial resistance. Moreover, the use of several surface modifiers, coating and stabilizing agents, resulted in enhancement of the bioactivity, rapid delivery and controlled drug release, improvement of biocompatibility and cytotoxicity. In this chapter, we have presented a comprehensive overview on the antimicrobial efficacy of noble metal nanoparticles along with the mechanistic insights behind their activity at a cellular and molecular level.

Making or formulation of nanoparticles for their commercialization prospect, more specifically for modulating nanomedicine and various biological applications, is now the most rapidly growing field in nanotechnology. Several companies are investing to develop various pharmaceutical applications on the basis of drug delivery, imaging and bio-diagnostic properties of the noble metal nanoparticles. Nanoparticles with drug delivery ability have been found as the most successful over other modes of treatment in the last few years. Even the exploitation is not only limited as antimicrobial, but NP is also found to be advantageous for cancer treatment.

Considering the COVID-19 pandemic, noble metal nanoparticles could be utilized as therapeutics as well as drug delivery vehicles. Some interesting findings on the efficacy of bioactive AgNPs and AuNPs against the antigenic proteins of SARS and MERS (Kim et al. 2018; Lin et al. 2019; Sekimukai et al. 2020) indicated that these nanoparticles could be the useful options to treat COVID-19. Particularly, rapid delivery of anti-SARS-CoV-2 antibody and/or vaccine could be aimed for COVID-19 treatment shortly.

Taken together, it is clearly evident that surface-modified noble metal nanoparticles, especially AgNPs and AuNPs, are advantageous for therapeutic uses due to their benign nature, broad-spectrum bioactivities, ability of conjugating/immobilizing several drugs/enzymes, tunable delivery and release of drugs, imaging/luminating potential and several other physio-biochemical attributes. Future research is therefore needing more emphasis in applying these nanoparticles
as in situ nanotrackers or nanobiosensors for diagnosing as well as treating life-threatening diseases of humans.

Acknowledgement BR and SM acknowledge all the collaborators with whom they have previously worked. RP thanks the Department of Higher Education, Govt. of West Bengal, for awarding Swami Vivekananda Merit Cum Means Fellowship.

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