Chapter 9
Gold Nanoparticles: A Lethal Nanoweapon Against Multidrug-Resistant Bacteria

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Abstract Multidrug-resistant (MDR) bacteria, also called superbugs, pose serious threat to the human health and existence because of their ability to develop resistant mechanism against commercially available antibiotics. Besides increasing the morbidity and mortality rate of patients, MDR bacteria are also putting huge financial stress on health sectors across the globe. It is estimated that approximately 700,000 people are losing their life every year due to MDR bacteria. It has been projected that more than 10 million people around the world will be the victim of MDR bacteria by 2050, if the current trend continues, superseding cancer as the main cause of global mortality. Hence, the mankind is in dire need to find an effective and safe tool against MDR bacteria.

Several metallic nanoparticles including Au, Ag, ZnO, and GO (graphene oxide) have shown antibacterial propensity against a wide range of bacteria. However, gold nanoparticles (AuNPs) received wide attention because of their inertness for the human body, easy surface fabrication properties, and optical properties. AuNPs demonstrate antibacterial activity through direct interaction with bacterial cell wall, generating reactive oxygen species (ROS), passing through the cell membrane and interacting with cellular macromolecules (i.e., DNA and proteins). In this chapter, we shall discuss different types of AuNPs, their role as potent antibacterial agents

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against pathogenic as well as multidrug-resistant bacteria, mechanism of antibacterial activity, biocompatibility, and future prospects in healthcare system.

Keywords Gold nanoparticles · Multidrug-resistant bacteria · Antibacterial activity · Biocompatibility

9.1 Introduction

Gold (Au) is an inert metal with distinct electronic and optical properties. When Au nanoparticles (AuNPs) are excited with light of a particular wavelength, the incident photons interact strongly with the conduction band of electrons and cause them to oscillate with resonant frequency. The collective oscillation is known as localized surface plasmon resonance (LSPR) that creates strong and localized electromagnetic fields and allows sensitive detection of changes in dielectric environment surrounding the surface of nanoparticles. This unique property makes them highly useful in imaging, drug delivery, cancer theranostics, and tackling menace of multidrug-resistant bacteria (Shankar et al. 2004; Mukherjee et al. 2001; Li et al. 2014). Au nanoparticles induce hyperthermia (i.e., increased temperature to kill cancer cells) upon illumination with near-infrared (NIR) light (Dash and Bag 2014; Huang et al. 2011). Furthermore, AuNPs can also be successfully and selectively delivered to malignant as well as benign tumors and can act as carriers for chemotherapeutic drugs. They are used as imaging agents as well as biosensors because of their ability to emit photons upon illumination (Marangoni et al. 2013).

The misuse and overuse of antibiotics have resulted in the emergence of multidrug-resistant bacteria, which is the cause of an additional medical costs of up to billion dollars every year (Rossolini et al. 2014; Li et al. 2014). Hence, suitable antibacterial agents to deal with multidrug-resistant bacteria are urgently needed. The antibacterial activity demonstrated by various nanomaterials including Ag, Au, Cu, Ti, ZnO_2, and MgO_2 could be a suitable alternative to commercially available antibiotics (Vimbela et al. 2017; Hossain et al. 2019; Niloy et al. 2020; Polash et al. 2021; Ranjan Sarker et al. 2019). More specifically, gold nanoparticles (AuNPs) have distinctive properties including their adjustable shape, size, surface properties, optical properties, high stability, biocompatibility, and multiple functionalization potential that make them suitable for different applications in the field of nanomedicine (Ashraf et al. 2016).

Based on the unique physical and chemical properties of nanoparticles, they provide a common platform for therapeutic applications against drug-resistant bacteria (Li et al. 2014). For example, AuNPs have already been used in the treatment of gum disease and dental caries, diagnosis of cancer, and in tissue engineering. Since AuNPs have antifungal and antibacterial activity, they can be conjugated with

biopolymers to improve their efficacy as bioactive materials (Bapat et al. 2020). In addition, AuNPs can also be used as carriers of antibacterial drugs. Antibacterial drugs are conjugated with AuNPs through chemical interactions so that drugs can be released at the desired site of action (Fan et al. 2019). Notably, AuNPs do not show toxic effects to normal cells at certain concentrations (Fang et al. 2019; Chatterjee et al. 2011). Therefore, it is possible to modify AuNPs that exhibit antibacterial activity against standard bacterial strains in general and have unique antibacterial activity against multidrug-resistant bacteria in particular (Su et al. 2020).

The recent development in nanoscience and nanotechnology has helped researchers to design and develop novel biomaterials including AuNPs with excellent bioactivity as well as biocompatibility. Many inorganic (i.e., metal) nanoparticles have been developed including AuNPs. The AuNPs show various colors based on their shape, size, and amount of aggregation of particles (Daniel and Astruc 2004). They are used in medical and pharmaceutical industries for various purposes: antibacterial agents, antibiofilm, diagnostic tools, drug delivery vehicles, personal care products, and for cosmetics development (Su et al. 2020; Abdalla et al. 2020). This chapter summarizes recent research works on the development of AuNPs and their application to tackle the menace of pathogenic and multidrug-resistant (MDR) bacteria.

9.2 Different Types of AuNPs

There are many different types of gold nanoparticles (AuNPs) depending on their size, shape, and physical properties (Fig. 9.1). Important AuNPs include Au nanospheres, nanorods, nanoshells, and nanocages. There is also another type of Au-based nanoparticles known as "SERS nanoparticles" with excellent surface-enhanced Raman scattering property. Most of the AuNPs are produced with well-defined size, shape, and monodispersity due to the continuous development of synthetic, and characterization techniques in the last two decades.

9.2.1 Au Nanospheres

The gold nanospheres, also known as gold colloids of 2 to 100 nm in diameter, can be synthesized through controlled reduction of an aqueous $HAuCl_4$ solution using different reducing agents under varying conditions. Citrate is the most widely used reducing agent that can produce nearly monodisperse gold nanospheres (Turkevich et al. 1951; Frens 1973). The size of the nanospheres can be controlled by changing the citrate to gold ratio. Generally, less amount of citrate generates larger nanospheres. The two major limitations of this method are the low yield and the obligation of using water as the solvent. A two-phase method, introduced by Faraday in 1857, capable of producing stable (irrespective of temperature and air) gold

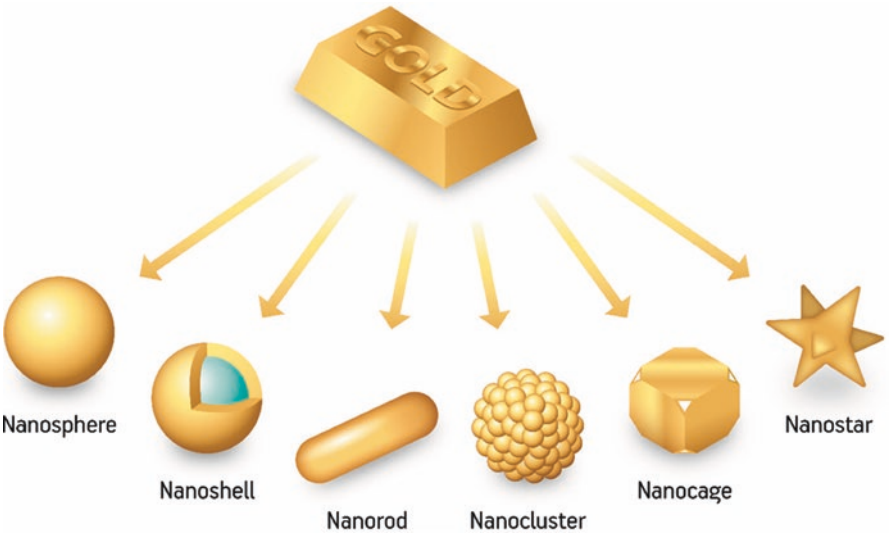

Fig. 9.1 Different types of AuNPs according to their shape and morphology. (Adapted from Freitas de Freitas et al. (2018))

nanospheres of reduced dispersity and defined size (i.e., 10 nm in diameter), was reported in 1993 (Giersig and Mulvaney 1993). The phase transfer reagent such as tetraoctylammonium bromide was used to improve this technique. Moreover, thiol/gold molar ratios can affect the average size of the nanospheres (Brust et al. 1994). Larger thiol-to-gold ratios and rapid addition of cold reductant solutions yield smaller and more monodispersed gold nanospheres. Many other methods have already been investigated for the synthesis of gold nanospheres using other reducing agents or ligands (Leff et al. 1996). On the other hand, dendrimers have been used as templates or stabilizers for the generation of Au nanospheres (Esumi et al. 1998). Biocompatible block copolymers have already been employed for the synthesis of sterically stabilized Au nanospheres in aqueous solution (Yuan et al. 2006). The shape and size of the Au nanospheres could be readily controlled by optimizing the synthesis parameters including block copolymer composition, relative/absolute concentrations of the block copolymer, and $HAuCl_4$. It was also reported that Au nanospheres could be grown in human cells (Anshup et al. 2005). Furthermore, Au nanospheres display a single absorption peak in the visible range between 510 nm and 550 nm. The absorption peak shifts to a longer wavelength with the increasing particle size, and the width of the absorption spectra is related to the size distribution range. Many other types of AuNPs with different size/shape including nanorods, nanoshells, and nanocages have been explored to obtain optical properties suitable for biomedical applications.

9.2.2 Au Nanorods

The Au nanorods have received worldwide attention because of their inimitable shape-dependent optical properties (i.e., different plasmon bands) that make the Au nanorods exclusive materials for biological imaging, sensing, photothermal therapy, and drug delivery (Hainfeld et al. 2008; Kodiha et al. 2014; Nichols and Bae 2014; Choi et al. 2010). Their application is very precise because even a small change in the shape, size, and surface nature alter their properties which in turn affect their biological applications. The surface plasmon resonance (SPR) band of Au nanorods is in the NIR region that makes them suitable for photothermal therapy, biological sensing, and imaging (Martin 1994). The Au nanorods can be synthesized using the template method. The diameter of the template membrane pore can be used to determine the diameter of the Au nanorods, while the length of the nanorods can be controlled through the amount of gold deposited within the pores. The main disadvantage of this method is low yield since only one monolayer of nanorods is prepared. The formation of Au nanorods through electrochemical synthesis has been also reported (Reetz and Helbig 1994; Yu et al. 1997; Chang et al. 1999). According to this approach, many experimental parameters determine the length of the Au nanorods that influence their aspect ratio which is defined as the length divided by the width. On the other hand, the seed-mediated synthesis, the most established method for Au nanorod preparation, provides higher aspect ratio than that prepared by the other methods (Jana et al. 2001a; Busbee et al. 2003). Usually, Au seeds are prepared by chemical reduction of Au salt (i.e., $HAuCl_4.3H_2O$) with a strong reducing agent including sodium borohydride (i.e., $NaBH_4$). These seeds, serving as the nucleation sites for Au nanorods, are then added to the growth solution containing Au salt, a weak reducing agent such as ascorbic acid, and hexadecyltrimethyl ammonium bromide. The aspect ratio of Au nanorods can be controlled by varying the amount of gold seeds with respect to the precursor. Furthermore, Au nanorods can be produced in quantitative yield upon addition of $AgNO_3$ (Jana et al. 2001b, 2002). Besides, several other types of approaches have also been investigated for the fabrication of Au nanorods including bioreduction (Canizal et al. 2001), growth on mica surface (Mieszawska and Zamborini 2005), and photochemical synthesis (Kim et al. 2006).

9.2.3 Au Nanocages

Gold (Au) nanocages are characterized by their ultrathin porous walls and hollow interiors. They are synthesized using silver nanoparticles (AgNPs) as template that participate in the galvanic replacement (GR) reaction (Skrabalak et al. 2007, 2008; Lu et al. 2007). The controllable pores on the surface of Au nanocages have been synthesized via galvanic replacement reaction between silver nanocubes and aqueous $HAuCl_4$ (Chen et al. 2006). The silver (Ag) nanostructures with controlled

morphologies can be generated through polyol reduction where $AgNO_3$ is reduced by ethylene glycol. Sequential addition of Ag atoms to the seeds produces the desired nanostructures by controlling Ag seed crystalline structures in the presence of poly(vinylpyrrolidone), a polymer capable of selectively binding to the surface. Ag nanostructures are used as supportive templates that can be transformed into Au nanostructures with hollow interiors via galvanic replacement (Chen et al. 2005, 2006). The wall thickness and dimension of the resultant Au nanocages could be readily controlled with high precision by adjusting the molar ratio of Ag to $HAuCl_4$ (Cai et al. 2008). The light penetration ability in soft tissues can be maximized by restricting the light source to near infrared (NIR) region (i.e., 650 to 900 nm). This is because the light absorption ability of hemoglobin and water is negligible in the NIR region. The LSPR peaks can be concisely tuned throughout the visible and NIR region to make the Au nanocages suitable for this application (Kwon et al. 2012; Mahmoud et al. 2010; Au et al. 2008; Mahmoud and El-Sayed 2010). Au nanocages can also be functionalized with the bioactive molecules to target cancer cells for diagnosis and photothermal therapy at an early stage (Dreaden et al. 2012; Chen et al. 2012).

9.2.4 Au Nanoshells

The Au nanoshells are composed of silica core coated by a thin Au metallic shell. The most interesting property of Au nanoshells is their unique surface plasmon resonance property that can be finely tuned from visible to NIR region. There are multiple templates employed for the formation of hollow Au nanoshells including silica particles (Averitt et al. 1997), metal particles (Oldenburg et al. 1998, Oldenburg et al. 1999a, b; Tuersun and Han 2013), and so on. The Au nanoshells have been applied in various biomedical applications such as whole-blood immunoassays and photothermal cancer therapy (Loo et al. 2005; Park et al. 2008; Bickford et al. 2010). Cancer cells were successfully ablated in vitro by Au nanoshells as observed through magnetic resonance thermal imaging. Furthermore, the use of Au nanoshells for the photothermal ablation of tumors in mice showed complete regression of tumors while the mice remain healthy (Gobin et al. 2007, 2008; Hirsch et al. 2003; Lowery et al. 2006). Optical imaging techniques including those that use AuNPs as the contrast agents have limited applications in human studies. On the other hand, in the NIR region (i.e., 700–900 nm), the absorbance of all the bioactive molecules is negligible which provides clear window for optical imaging (Frangioni 2003). Au nanoshells can be designed and fabricated to control the location of surface plasmon resonance (SPR) peaks from visible to the NIR region of the electromagnetic spectrum by varying the composition and dimensions of the layers (Oldenburg et al. 1999a). The SPR peak can also be tuned by changing the ratio of the core size to its shell thickness for a given composition of Au nanoshells. Furthermore, Au nanoshells with SPR peaks in the NIR region can be prepared by coating Au shells with silica or polymer beads of variable thickness (Oldenburg et al. 1998; Caruso

et al. 2001). The silica cores are grown according to the Stöber process, that is, the reduction of tetraethyl orthosilicate in basic ethanol. A seed-mediated growth technique is typically used to coat the silica nanoparticles with Au in an aqueous environment. The small Au nanospheres, such as 2–4 nm in diameter, can be attached to the silica core using an amine-terminated silane as a linear molecule that allows additional Au to be reduced until the seed particles coalesced into a complete shell (Oldenburg et al. 1999b). The diameter of the gold nanoshells is mainly determined by the diameter of the silica core, and the shell thickness can be controlled through the amount of gold deposited on the surface of the core. Gold nanoshells have also been synthesized via in situ gold nanoparticle formation using thermosensitive core-shell particles as the template (Suzuki and Kawaguchi 2005). The use of different microgels as the core offers significantly reduced particle aggregation. The thickness of Au nanoshells was also controlled through electroless deposition of Au. Recently, a virus scaffold has been used to assemble Au nanoshells which may potentially provide cores with a narrower size distribution and smaller diameters (i.e., 80 nm) than that of silica (Radloff et al. 2005).

9.2.5 Au Nanostars

Gold (Au) nanostars belong to the anisotropic AuNPs category. Au nanostars are composed of a core and several branches with sharp tips. The unique characteristics of Au nanostars originate from these branches and their interaction with the core. The attractive features of Au nanostars are localized surface plasmon resonance (LSPR), surface-enhance Raman Scattering (SERS) activity, and catalytic activity. The Au nanostars are used for catalysis, nanosensing assays, thermal therapy, and drug delivery. The Au nanostars have multiple sharp branches that demonstrate significant electromagnetic field enhancement and have unique plasmon bands which can be tuned from visible to NIR region. The synthesis of Au nanostars has been driven by the interest on the localized surface plasmons (LSPs) response to the environment, especially on sharp tips and edges, where light can be highly concentrated (Hao et al. 2007; Rodríguez-Lorenzo et al. 2009; Hrelescu et al. 2009; Dondapati et al. 2010). They serve as effective tools in the field of nanomedicine due to their unique properties. The Au nanostars also display stronger surface-enhanced resonance activity than Au spheres or even rods (Mukherjee et al. 2001; Cai et al. 2008).

9.3 Antibacterial Activity of AuNPs

Although gold nanoparticles (AuNPs) are not strong antimicrobial agent as AgNPs, they have been reported to demonstrate antibacterial (Lima et al. 2013) as well as antifungal activity (Wani and Ahmad 2013; Zawrah et al. 2011). Furthermore,

AuNPs have been used as an alternative tool to high-dose antibiotics against infectious diseases including antibiotic-resistant bacteria (Podsiadlo et al. 2008). The nanoparticle toxicity and antibacterial activity mainly depend on the intrinsic properties, surface modification, and tested bacterial species. The AuNPs of smaller diameter can penetrate the bacterial cells and cause cellular damage followed by death (Bindhu and Umadevi 2014a). Antibacterial properties of triangular-shaped AuNPs demonstrate better activity toward both gram-positive and gram-negative bacteria than that of spherical AuNPs (Smitha and Gopchandran 2013). The sharp-faced triangular NPs, irrespective of their surface chemistry, size, and composition, can pierce the endosomal membrane before translocating to the cytoplasm where they can be retained. This feature makes them preferable to round-shaped NPs for drug delivery, gene delivery, subcellular targeting, and long-term tracking (Chu et al. 2014). Recently, it has been reported that very small AuNPs (i.e., less than 2 nm) showed excellent antibacterial activity against gram-positive and gram-negative bacteria (Kundu 2017).

9.3.1 Antibacterial Activity Against Pathogenic Bacteria

The AuNPs synthesized using citrate, polyvinylpirrolidone (PVP), or other commonly used stabilizers usually do not show antibacterial activity (Amin et al. 2009). More specifically, the AuNPs (size: 20–30 nm) stabilized by PVP and/or sodium dodecyl sulfate (SDS) did not show antimicrobial activity against *Staphylococcus aureus* ATCC 6538, *Escherichia coli* K12 NCTC 10538, and fungi *Candida albicans* ATCC 10231 at a concentration of 0.0016 wt% (Mukha et al. 2010). Chatterjee et al. (2011) found that AuNPs showed no concentration-dependent antibacterial activity while stimulating the level of cell division. AuNPs are biologically inert and usually do not show antibacterial activity (Allahverdiyev et al. 2011) that can be convinced from their high MIC value and small zone of inhibition (ZOI) value when compared to AgNPs. Hernández-Sierra et al. (2008) compared the antibacterial activity of AgNPs (size: 25 nm) with that of AuNPs (size: 80 nm) against *S. aureus* ATCC 25923. The AgNPs had a MIC (minimum inhibitory concentration) value of 4.86 ± 2.71 μg/ml and MBC (minimum bactericidal concentration) value of 6.25 μg/ml. On the other hand, AuNPs showed antibacterial propensity at a very high concentration (197 μg/ml). Shankar et al. (2014) synthesized AuNPs, AgNPs, and Au-AgNPs having hydrodynamic size 140 ± 13, 74 ± 6, and 128 ± 15 nm, respectively. The growth of *S. aureus* and *E. coli* was inhibited at 16 μg/ml and 8 μg/ml of AgNPs, respectively. Similar pattern of inhibition was also observed for Au-AgNPs having MIC value 16 and 32 μg/ml against *S. aureus* and *E. coli,* respectively. On the other hand, AuNPs did not show any antibacterial activity at the tested concentration (i.e., 128 μg/ml). Sreelakshmi et al. (2011) compared the antibacterial activity of AuNPs and AgNPs (size: 10 nm) synthesized using natural honey as a source of stabilizing as well as reducing agent. Their MIC values confirmed that honey-capped AgNPs exhibit very good antibacterial activity, whereas AuNPs exhibit

moderate activity against the tested strains. On the other hand, PVP-coated AuNPs have ~10 times higher MIC value than that of AgNPs synthesized using the same polymer (Mukha et al. 2010; Hernández-Sierra et al. 2008). Hence, AuNPs are not usually used as antibacterial agents. In addition, incorporation of AuNPs (2 nm), methylene blue (MB), and toluidine blue (TBO) with polyurethane polymer, a polymer used to prepare catheters, enhanced the killing of *S. aureus* suspension under white illumination with a hospital light source (Naik et al. 2011). However, many other studies have revealed that AuNPs synthesized under certain conditions showed efficient antibacterial activity and they can be functionalized with different biopolymers to make an effective antibacterial agent. The size, shape, surface modification (coating and capping agents), and purification methods of AuNPs are the key factors that determine their antibacterial activity. However, CTAB-coated AuNPs of 1~2 nm and 1~20 nm in size were reported to show similar zone of inhibition (~22 mm) against *E. coli* (ATCC 25922 strain) without any size dependence (Azam et al. 2009; Arshi et al. 2011).

Furthermore, Badwaik et al. (2012) investigated the antibacterial activity of dextrose-coated AuNPs having different hydrodynamic diameters such as 25, 60, and 120 ± 5 nm. AuNPs with hydrodynamic diameter of 120 and 60 nm inhibit the proliferation of *E. coli* in a concentration-dependent manner and the MIC values were 16×10^{10} and 16×10^{11} particles/ml, respectively. On the other hand, AuNPs having 25 nm hydrodynamic diameter did not show any significant effect against the proliferation of *E. coli* even at concentration as high as 128×10^{12} particles/ml. Hence, they concluded that the antibacterial activity of AuNPs increases as the particle size increases, for example, in the order of 25 < 60 < 120 < nm. On the other hand, Ahmad et al. reported that smaller AuNPs (i.e., 7 nm) showed excellent antifungal activity and greater biocidal effect against *Candida* species when compared to that of relatively large AuNPs (i.e., 15 nm) (Ahmad et al. 2013). The capping agent is also an important determinant of the antibacterial activity of AuNPs. Zhang et al. (2008) synthesized hyperbranched poly(amidoamine) having terminal dimethylamine groups (HPAMAM-N $(CH_3)_2$) to prepare AuNPs and they found that the cationic dimethylamine contributes to the antimicrobial activity through strong ionic interactions with bacteria. As shown in Table 9.1, AuNPs stabilized or modified by various coating agents have distinct antibacterial effects. Many small molecules were also used for the synthesis of AuNPs and were investigated for their antibacterial potential. For example, 4, 6-diamino-2-pyrimidinethiol (DAPT), an analogue of 2-pyrimidinethiol that is present in *E. coli*; two positively charged and amino-substituted pyrimidines 4-amino-2-pyrimidinethiol and 2,4-diamino-6-pyrimidine thiol (iDAPT) (Chatterjee et al. 2011); and one negatively charged pyrimidine 4,6-dihydroxyl-2- pyrimidine thiol (DHPT) (Zhao et al. 2010) were used to fabricate AuNPs. The MIC values of DAPT, APT, and iDAPT fabricated AuNPs against *Pseudomonas aeruginosa* were 16, 18, and 24 μg/ml, respectively. DHPT-coated AuNPs did not inhibit the growth of both *E. coli* and *P. aeruginosa* even at high concentration (80 μg/ml).

The methods used for the purification of AuNPs were neither mentioned nor adequately carried out before performing antibacterial assay. There could be debate

Table 9.1 A summary of the antibacterial activity of AuNPs synthesized using different types of reducing agents and capping agents

AuNPs (reducing agents and capping agents)	Size (if present)	Test bacteria	Effect of antibacterial activity	Ref.
Citric acid Polyallylamine HCl	20–30 nm	*B. Calmette-Guérin* *E. coli*	Effect and mechanism depend upon composition and surface modifications	Zhou et al. (2012)
Citrate/CTAB	1–22 nm	*E. coli*	AuNPs show high antibacterial activity with zone of inhibition of 22 mm	Zhang et al. (2015)
Acridine derivatives	15–20 nm	*E. coli* *Bacillus subtilis*	Acridine-AuNPs has stronger antibacterial effect than acridine alone	Mitra et al. (2014)
Citrate	20–30 nm	*E. coli*	Dose-dependent inhibition, 0.1–5 μg/mL	Zhou et al. (2012)
Phosphine	–	*S. aureus*	Antibacterial activity of two ligands are compared	Borah et al. (2011)
Pyrimidine thiols	3 nm	*P. aeruginosa*	MICs of Au-DAPT, Au-APT, and Au-iDAPT are 16, 18, and 24 μg/mL	Zhao et al. (2010)
Thioguanine	–	*Micrococcus luteus* *S. aureus* *P. aeruginosa* *E. coli*	AuNPs are more potent than thioguanine	Selvaraj et al. (2010)
PVP/SDS	20–30 nm	*S. aureus* *E. coli* K12	AuNP of 0.0016% wt. showed no effect on tested strains	Mukha et al. (2010)
Gallic acid	14, 39, 77 nm	*S. mutans*	MICs of 12.31, 12.31, and 49.25 μg /mL for 13.7, 39.4, and 76.7 nm AuNPs	Moreno-Álvarez et al. (2010)
Reduced by lysozyme at 40 °C	–	*Acinetobacter baumannii* *Enterococcus faecalis*	Broad-band labeling agents for pathogenic bacteria	Chen et al. (2010)
Citrate, CTAB	1 ~ 22 nm	*E. coli*	Zone of inhibition of 22 mm	Arshi et al. (2011), Zhang et al. (2015)
Polyamidoamine	7.7, 4.6, 3.9 nm	*E. coli* *S. aureus* *B. subtilis* *Klebsiella mobilis*	Inhibit up to AuNP (2.8 μg/mL) Ionic interaction with bacteria	Zhang et al. (2008)
PVP	80 nm	*S. aureus*	MIC, > 197 μg/mL	Hernández-Sierra et al. (2008)

(continued)

Table 9.1 (continued)

AuNPs (reducing agents and capping agents)	Size (if present)	Test bacteria	Effect of antibacterial activity	Ref.
Polythiophene composite	–	Common bacterial pathogens	Efficient antibacterial effect was observed	Adhikari et al. (2013)
Citrate or PAH	2–30 nm	*E. coli*	*E. coli* growth inhibited at 0.1, 1, 5 μg/mL citrate-AuNPs	Zhou et al. (2012)
Capped by amine or polyacrylate	–	*E. coli*	99.999% killing in 10 min. Coating agents are responsible for antibacterial activity	Wan and Yeow (2012)
Dextrose	25, 60, and 120 nm	*E. coli*	For 120 and 60 nm AuNPs with MIC 16 × 1010 and 16 × 1011 NPs/mL for 25 nm AuNPs, no inhibition at 128 × 1012 NPs/mL	Badwaik et al. (2012)
Cationic peptides	1.2–2.5 nm	*S. aureus* *B. subtilis* *E. coli* *P. aeruginosa*	MIC higher with AuNP than without	Pal et al. (2011)
Zeolite (2.3–2.8%)	5 nm	*E. coli* *Salmonella typhi*	Eliminate 90–95% of *E. coli* and *S. typhi* colonies at short time	Lima et al. (2013)
Polyoxometalates and lysine	–	*E. coli*	5 μM causes 80% bacterial death	Daima et al. (2013)
Cationic monolayer	2 nm	MDR strains and MRSA	MIC values dependent on side chain functional groups and chain length	Li et al. (2014)
Zeolite	–	*E. coli* *S. Typhi*	AuNPs dispersed on zeolites eliminate *E. coli* and *S. typhi* at short times	Zhang et al. (2015)

on the antibacterial activity of AuNPs because of the presence of capping agents or other reagents used for the synthesis of nanoparticles that were not purified properly. It might be, therefore, the presence of Au(III) ions as well as unreacted reagents interfere with the antibacterial results, thereby producing false results. Several studies have reported the purification of chemically synthesized AuNPs prior to investigating their antimicrobial activity. For example, Daima et al. synthesized tyrosine-functionalized AuNPs and dialyzed to remove free ions and unbound tyrosine prior to investigating their antibacterial activity to avoid any interference on their toxicity bacteria (Daima et al. 2013). Furthermore, Zhou et al. (2012) prepared citrate-stabilized AuNPs followed by purification through centrifugation to test antibacterial activity against *E. coli* and *Bacillus Calmette-Guérin.* Nazari et al. also reported the synthesis and purification of AuNPs before testing their antibacterial activity against *P. aeruginosa, S. aureus*, and *E. coli* (Nazari et al. 2012).

On the other hand, AuNPs were also synthesized and fabricated using natural polymers extracted from either microorganisms or plants, or directly in the presence of microorganisms. They are summarized in Table 9.2. These processes are known as green or eco-friendly synthesis or biosynthesis. For instance, Nagaraj et al. (2012) synthesized spherical AuNPs (size: 10–50 nm) using *Caesalpinia pulcherrima* flower extract as the reducing agent that showed efficient antimicrobial activity against *Aspergillus*, *E. coli*, and *Streptobacillus* sp. Das et al. (2009) synthesized AuNPs (size: 10 nm) on the surface of *Rhizopus oryzae* MTCC 262 through in situ reduction of $HAuCl_4$ that showed high antibacterial activity against several gram-positive and gram-negative pathogenic bacteria. Mishra et al. (2011) synthesized AuNPs (size: 50–70 nm) and AgNPs (size: 10–20 nm) via extracellular synthesis using yeast *Candida guilliermondii* and the highest antibacterial activity for both AuNPs and AgNPs was found against *Staphylococcus aureus*. AuNPs were also synthesized using various plant extracts including *Mentha piperita* (MubarakAli et al. 2011*)*, root extract of *Trianthema decandra,* (33–65 nm) (Geethalakshmi and Sarada 2012), *Helianthus annuus* flower extracts (Geethalakshmi and Sarada 2012), and dried flower extract of *Carthamus tinctorius* (Liny et al. 2012). Interestingly, all the green synthesized AuNPs demonstrated efficient antibacterial activity against several bacteria strains that were unaffected in the presence of chemically synthesized AuNPs (Mishra et al. 2011). Finally, the question is what is responsible for the antibacterial activity of green-synthesized AuNPs. It may be due to the extracts alone, AuNPs or their combination with plant extracts, since several plant extracts including *Euphorbia hirta* plant alone demonstrated antibacterial activity (Annamalai et al. 2013). Hence, the antibacterial activity may also be due to the synergistic effect of the combination of AuNPs and extracts (Annamalai et al. 2013).

9.3.2 Antibacterial Activity Against Multidrug-Resistant (MDR) Bacteria

Metallic gold is inert and non-toxic that may change when shifts from metallic to oxidation states (0, I, and III) (Merchant 1998). The antibacterial mechanism of AuNPs is associated with (i) the collapse of membrane potential that inhibits the ATPase activity and causes deterioration of the cellular metabolism and (ii) inhibition of the binding subunit of ribosomes to tRNA (Cui et al. 2012). Also (iii) Shamaila and co-workers showed that AuNPs disrupt the bacterial respiratory chain by binding to the thiol group of enzymes including nicotinamide adenine (NADH) dehydrogenase and produce oxidative stress resulting in the cellular death (Shamaila et al. 2016). Since AuNPs are non-toxic to the host (Li et al. 2014; Conde et al. 2014; Rajchakit and Sarojini 2017), the possibility of fine-tuning their conjugation ability to act as carriers of antibiotics or other antibacterial moieties may enhance their bactericidal effect as well as potentiate the effect of antibiotics (Baptista et al. 2018). Functionalization of AuNPs with cationic and hydrophobic polymers was

Table 9.2 A summary of antibacterial activity of AuNPs synthesized using "green" method

AuNPs (green method)	Size (if present)	Test bacteria	Effect of antibacterial activity	Ref.
Black tea extract	2–100 nm	*P. aeruginosa* *S. aureus* *E. coli*	AuNPs did not increase antibacterial activity at concentration of 40 µg/disc	Nazari et al. (2012)
Shewanella oneidensis	12 ± 5 nm	*E. coli* *S. oneidensis* *B. subtilis*	No bactericidal effect for the tested strains at concentrations of 150 µM	Suresh et al. (2011)
Punica Granatum	5–17 nm	*S. aureus* *S. typhi* *Vibrio cholerae*	MIC values for the tested bacteria – 0.33, 0.37 and 0.41 mg/mL	
C. zeylanicum leaf broth	>100 nm	*E. coli* *S. aureus*	Efficient antibacterial activity	Smitha and Gopchandran (2013)
Memecylon umbellatum leaf	15–25 nm	*B. subtilis* *E. coli* S. *pneumoniae* *S. aureus* *S. typhimurium* *K. aerogenes*	Inhibited bacterial growth	Arunachalam et al. (2013)
E. hirta	6–71 nm	*E. coli* *P. aeruginosa* *K. pneumoniae*	Complete inhibition at a concentration of 200 µg/mL	Annamalai et al. (2013)
T. decandra	33–65 nm	*P. vulgaris* *E. coli* *S. aureus* *S. faecalis*	Excellent activity at a concentration of 10 mg/L on each disc	Geethalakshmi and Sarada (2012)
Solanum nigrum	18–20 nm	*B. subtilis* *E. coli* *P. aeruginosa*	Inhibited bacteria growth	Balagurunathan et al. (2011)
Phyllanthus emblica	2–4 nm	*S. aureus* *E. coli*	Zone of inhibition, 0.8–1.0 cm	Balasubramanian (2014)
Gracilaria corticata	45–57 nm	*S. aureus* *E. faecalis* *E.coli* *Enterobacter aerogenes*	Antimicrobial activity observed for tested bacteria at 24, 21, 19 and 14 mm	Naveena and Prakash (2013)
Phytochemicals	15–35 nm	*E. coli* *B. subtilis* *S. aureus* *Enterococci*	AuNPs showed zone of inhibition against all the studied bacteria	Mahitha et al. (2013)
Soybean Polyphenols	7–12 nm	*S. aureus* *P. aeruginosa* *A. baumannii*	Gram-negative bacteria with thin cell wall were more susceptible to cell wall damage compared to gram-positive bacteria	El-Batal et al. (2013)

(continued)

Table 9.2 (continued)

AuNPs (green method)	Size (if present)	Test bacteria	Effect of antibacterial activity	Ref.
Rhizopus oryzae MTCC 262	10 nm	*P. aeruginosa* *E. coli* *B. subtilis* *S. aureus*	Inhibition starts at 50 μg/mL caused rupture of cell membrane	Das et al. (2009)
Saururus chinensis leaf	–	*S. aureus* *E. coli*	27.6% inhibition with AuNPs of 0.2 mM and >90% inhibition after 24 h exposure at AuNPs of 0.8–1 μM	Sreekanth et al. (2012)
Reduced by *C. tinctorius* flower	–	*S. aureus* *E. coli* *B. subtilis*	Efficient antibacterial effect was observed	Nagajyothi et al. (2012)
Treatment with root extract of *T. decandra*	33–65 nm	*E. faecalis* *S. aureus* *S. faecalis* *B. subtilis* *Y. enterocolitica* *P. vulgaris* *E. coli* *P. aeruginosa*	Inhibition areas (mm) for *E. faecalis* 10.5, *S. aureus* 14.5, *S. faecalis* 13.5, *B. subtilis* 9.5, *Y. enterocolitica* 15.5, *P. vulgaris* 15.0, *E. coli* 9.5, *P. aeruginosa* 11.5	Geethalakshmi and Sarada (2012)
Ananas comosus	–	*E. coli* *Streptobacillus sp*	Effective on *E. coli* & *Streptobacillus sp*	Basavegowda et al. (2013)
Euphorbia hirta	6–71 nm	*E. coli* *P. aeruginosa*, *K. pneumoniae*	Inhibited 88% *E. coli*, 86% *P. aeruginosa*, and 94% *K. pneumoniae* at 200 μg/mL; plant *E. hirta* has antibacterial activity itself	Annamalai et al. (2013)
Solanum torvum	–	*E. coli* *Pseudomonas* *Bacillus*	AuNPs showed strong and fair zone of inhibition	Ramamurthy et al. (2013)
Dioscorea batatas	18–56 nm	Gram-positive and gram-negative bacteria	AuNPs inhibited *S. aureus*, *S. epidermidis*, *E. coli*; 21.5% inhibition by 0.2 μM and >50% by 0.8–1 μM AuNPs	Sreekanth et al. (2015)
LD fruit peel	140, 74, 128 nm	*S. aureus* *E. coli*	No antibacterial activity at >128 μg/mL for AuNPs, but for AgNPs and Au-Ag-NPs	Shankar et al. (2014)

(continued)

Table 9.2 (continued)

AuNPs (green method)	Size (if present)	Test bacteria	Effect of antibacterial activity	Ref.
Abelmoschus esculentus	14 nm	*B. subtilis* *B. cereus* *P. aeruginosa* *M. luteus* *E. coli*	AuNPs (0.2 mg/mL) showed inhibition zones of 26, 24, 15, 35 and 21 mm against *B. subtilis*, *B. cereus*, *E. coli*, *M. luteus*, *P. aeruginosa*	Mollick et al. (2014)
Trichoderma viride, Hypocrea lixii	61 nm	*E. coli* *Shigella sonnei* *P. syringae*	Inhibition of the growth of *E. coli*, *S. sonnei*, and *P. syringae* up to 53%, 47%, 55%	Mishra et al. (2014)
Punica granatum	5 and 20 nm	*S. aureus* *S. typhi* *V. cholerae*	MICs against *S. aureus*, *S. typhi*, *V. cholerae* are 0.33, 0.37, 0.41 mg/mL	Lokina et al. (2014)
Solanum lycopersicums	14 nm	*S. aureus* *P. aeruginosa*	Effective inhibition of growth of all tested bacteria	Bindhu and Umadevi (2014b)
Mentha piperita	150 nm	*E. coli* *S. aureus*	Effective against *aureus* *E. coli,* but not *S. aureus*	MubarakAli et al. (2011)
Candida guilliermondii	50–70 nm	Five pathogenic bacterial strains	Highest inhibition against *S. aureus*; chemically synthesized AuNPs showed no effect	Mishra et al. (2011)
Trianthema decandra or saponin	37.7–79.9 nm	10 different bacteria	Zones of inhibition of 8.2 mm to 11.5 mm; excellent activity against *Y. enterocolitica*, *P. vulgaris*, *E. coli*, *S. aureus*, *S. faecalis*	Geethalakshmi and Sarada (2013)
Grapes fruit	–	*P. aureus* *S. typhi* *V. cholerae*	Excellent antibacterial activity toward most of the tested bacterial strains	Lokina et al. (2014)

shown to be effective against both gram-negative and gram-positive uropathogens including MRSA. These AuNPs exhibited low toxicity to mammalian cells, and development of resistance to these nanoparticles was very low (Li et al. 2014). Vinoj et al. demonstrated that the conjugation of AuNPs with N-acylated homoserine lactonase proteins (AiiA AuNPs) resulted in a nano-composite with greater antibacterial activity against MDR species when compared to AiiA proteins alone (Vinoj et al. 2015).

The integration of AuNPs on the shell of PVA-lysozyme microbubbles demonstrated better antibacterial potential against *E. coil* than that of only microbubbles (Mahalingam et al. 2015). Galic acid–capped AuNPs have also been found to be active against gram-negative and gram-positive bacteria (Kim et al. 2017). Recently, Ramasamy et al. reported one-pot synthesis of cinnamaldehyde-immobilized gold

nanoparticles (CGNPs) having more than 80% effectivity against biofilm formation of gram-positive (methicillin-sensitive and -resistant strains of *S. aureus*, MSSA, and MRSA, respectively) and gram-negative (*E. coli and P. aeruginosa*) bacteria (Ramasamy et al. 2017a, b). The incorporation of AuNPs with ultrathin graphitic carbon nitride (g-C_3N_4) generates peroxidase activity and demonstrates excellent antibacterial potential against drug-resistant (DR) gram-positive and gram-negative bacteria. They also exhibit high efficiency in eliminating existing DR biofilms and preventing the formation of new biofilms in vitro (Wang et al. 2017a). The conjugation of antibiotics (e.g., vancomycin and methicillin) to AuNPs increases their intrinsic activity against MDR strains (Baptista et al. 2018). Recently, Payne et al. developed a single-step synthesis technique for kanamycin-capped AuNPs (Kan-AuNPs) that exhibit high antibacterial activity against both gram-positive and -negative bacteria including kanamycin-resistant bacteria. The authors observed a significant reduction in the MIC value against all the bacterial strains tested when compared to free drug. This higher efficacy was due to the disruption of the bacterial envelope that resulted in the leakage of cytoplasmic content and thereby cell death (Payne et al. 2016). Pradeepa et al. synthesized AuNPs using bacterial exopolysaccharide (EPS) and functionalized them with antibiotics (e.g., levofloxacin, cefotaxime, ceftriaxone, and ciprofloxacin). They observed that antibiotic-conjugated AuNPs exhibited excellent bactericidal activity against MDR gram-positive and -negative bacteria when compared to free drugs. *E. coli* was the most susceptible MDR bacteria followed by *K. pneumoniae* and *S. aureus* (Vidya et al. 2016). Recently, Yang et al. described the effect of small molecule (6-aminopenicillanic acid, APA) coated AuNPs to inhibit MDR bacteria (Yang et al. 2017). They conjugated AuNPs with electrospun fibers of poly(ε-caprolactone) (PCL)/gelatin to produce materials that inhibit wound infection by MDR bacteria and also demonstrated that APA-AuNPs reduce MDR bacterial infections (Yang et al. 2017). Shaker et al. evaluated the surface functionalization of AuNPs with carbapenems [i.e., imipenem (Ipm) and meropenem (Mem)] and investigated their antibacterial activity against carbapenem-resistant gram-negative bacteria isolated from an infected human. Both Ipm-AuNPs and Mem-AuNPs (size: 35 nm) showed significant increase in their antibacterial activity against all the tested isolates (Shaker and Shaaban 2017). Recently, Shaikh et al. described the synthesis and characterization of cefotaxime-conjugated AuNPs to target drug-resistant CTX-M-producing bacteria. The authors inverted resistance in cefotaxime-resistant bacterial strains (i.e., *E. coli* and *K. pneumoniae*) by using cefotaxime-AuNPs. Hence, the conjugation of unresponsive antibiotics with AuNPs can restore their antibacterial activity against drug-resistant bacterial strains (Shaikh et al. 2017).

One of the most important properties of AuNPs is their ability to generate heat upon illumination with laser (Mendes et al. 2017; Mocan et al. 2017). This property is very important because it can be exploited to develop photothermal nano-vectors to destroy MDR bacteria at the molecular level (Mocan et al. 2017). For example, Khan et al. showed that the combination of Concanavalin-A (ConA)-directed dextran capped AuNPs (GNP_{DEX}-ConA) conjugated with methylene blue (MB) (MB@GNP_{DEX}-ConA)-mediated photodynamic therapy (PDT) enhanced the efficacy and

selectivity of MB-induced killing of MDR clinical isolates including *E. coli, K. pneumoniae, and Enterobacter cloacae* (Khan et al. 2017). Gil-Tomas et al. reported that the covalent conjugation of AuNPs with toluidine blue O–tiopronin forms an enhanced and exceptionally potent antimicrobial agent when activated by white light or 632 nm laser light (Gil-Tomás et al. 2007).

Hu et al. modified the surface of AuNPs with pH-responsive mixed charged zwitterionic self-assembled monolayers composed of weak electrolytic 11-mercaptoundecanoic acid (HS-C10-COOH) and strong electrolytic (10-mercaptodecyl) trimethylammonium bromide (HS-C10-N4) that exhibited an enhanced photothermal ablation of MRSA biofilm without any damage to the healthy tissues around the biofilm when illuminated with near infrared (NIR) laser (Hu et al. 2017). Furthermore, the antibacterial activity of glucosamine-gold nanoparticle-graphene oxide (GlcN-AuNP-GO) and UV-irradiated GlcN-AuNP-GO was evaluated against *E. coli* and *E. faecalis*. UV irradiation of GlcN-AuNP-GO demonstrated higher antibacterial activity than antibiotic kanamycin (Govindaraju et al. 2016).

Ocsoy et al. developed DNA aptamer-functionalized AuNPs (Apt@AuNPs) and gold nanorods (Apt@AuNRs) to kill methicillin-resistant *Staphylococcus aureus* (MRSA) through photothermal therapy (PTT) (Ocsoy et al. 2017). They found that both Apt@AuNPs and Apt@AuNRs attached to MRSA and inactivated cells by 5% and > 95%, respectively, through PTT. The difference in the induction of cell death was based on the relatively high longitudinal absorption of NIR radiation and strong photothermal conversion capability of the Apt@AuNRs compared to Apt@AuNPs. Recently, a new approach based on the conjugation of AuNPs with antimicrobial peptides (AMPs) has shown promising results (Rajchakit and Sarojini 2017). For example, Kuo et al. mixed synthetic peptides containing arginine, tryptophan, and cysteine termini [i.e., (DVFLG) 2REEW4C and (DVFLG) 2REEW2C] with aqueous tetrachloroauric acid to generate peptide-immobilized AuNPs [i.e., (DVFLG) 2REEW4C-AuNPs and (DVFLG) 2REEW2C-AuNPs] that were effective against *Staphylococci*, *Enterococci*, and other antibiotic-resistant bacterial strains (Kuo et al. 2016). Conjugation of AMPs with AuNPs usually involves the formation of Au-S coordinate covalent bond between the amine and thiol groups of peptides or conjugating linkers as well as terminal (N- or C-terminal) cysteine of AMPs which help in their conjugation with gold (Tielens and Santos 2010; Xue et al. 2014). However, there is one example when covalent conjugation of an AMP to AuNPs has been achieved via Au-O bond (Lai et al. 2015). Other approaches used a polyethylene glycol linker to covalently attach AMPs with AuNPs that showed significantly increased antibacterial and anti-biofilm activity against antibiotic-resistant gram-negative bacteria (Casciaro et al. 2017). Yeom and co-workers demonstrated the most advanced clinical application for AuNPs@AMP using infected mice in vivo that resulted in the inhibition of *Salmonella typhi* colonization in the organs of the animals (Yeom et al. 2016). The reason behind the increased antimicrobial activity of AuNPs@AMP over the free AMPs is that AuNPs can get a higher concentration of the peptides at the site of action. These NPs interact with lipopolysaccharides (LPS) and proteins of bacterial membrane and, in some cases, penetrate the

bacterial membrane through the porin channel. Thus, the nanoparticles interact with the bacterial inner membrane making the AuNPs@AMP conjugate more efficient than the non-conjugated form (Baptista et al. 2018). Rai et al. demonstrated the conjugation of cecropin-melittin (CM-SH), a known peptide with inherent antibacterial propensity (Boman et al. 1989), with the surface of AuNPs through Au-S bond. The CM-SH-AuNPs showed greater antimicrobial activity in a systemic (i.e., animal) model than CM-SH (Rai et al. 2016) (Table 9.3).

Table 9.3 Mechanism of antibacterial activity of AuNPs against multidrug-resistant (MDR) bacteria

Type of antibiotic resistance	Targeted bacteria	Mechanisms of antibacterial activity of AuNPs	Ref.
Methicillin resistant	*S. aureus*	Photothermal therapy with ROS generation	Hu et al. (2017), Ocsoy et al. (2017), Kuo et al. (2009), Millenbaugh et al. (2015), Mocan et al. (2016)
Methicillin resistant	*E. faecalis*	Combination with vancomycin	Lai et al. (2015)
Ampicillin resistant	*S. aureus, E. coli, P. aeruginosa, Enterobacter aerogenes*	Combination with ampicillin lead to entry into the bacterial cell	Brown et al. (2012)
Carbapenems resistant	*Klebsiella pneumoniae, Proteus mirabilis, A. baumannii*	Disturbance of osmotic balance and disruption of the integrity of bacterial cell wall	Shaker and Shaaban (2017)
Cefotaxime resistant	*E. coli, K. pneumoniae*	Disruption of the bacterial cell wall, DNA damage	Shaikh et al. (2017)
Kanamycin-resistant	*Streptococcus bovis, S. epidermidis, E. aerogenes*	Disruption of the bacterial cell wall	Payne et al. (2016)
Biofilm formation	*P. aeruginosa*	Interaction with cell surface	Yu et al. (2016)
Biofilm formation	*S. aureus*	Laser excitation of the near IR LSPR led to an efficient photothermal response with efficient killing of bacteria biofilms	Pallavicini et al. (2014)
Biofilm formation	*S. epidermidis, S. haemolyticus*	Combination with antibiotics	Roshmi et al. (2015)
Biofilm formation	*E. coli, P. aeruginosa, S. aureus*	Penetration through biofilm layers and interaction with cellular components	Ramasamy et al. (2017a, b)

(continued)

Table 9.3 (continued)

Type of antibiotic resistance	Targeted bacteria	Mechanisms of antibacterial activity of AuNPs	Ref.
Biofilm formation	*E. coli*, *P. aeruginosa*, *S. aureus*, *B. subtilis*	ROS generation	Wang et al. (2017a)
Biofilm formation	*Proteus* species	Interaction between proteins and NPs	Vinoj et al. (2015)
Multidrug resistant	Gram-negative bacteria	Automated microarray-based system for early identification of pathogen and resistance marker detection	Walker et al. (2016)
Multidrug resistant	*E. coli, S. aureus, K. pneumoniae*	Combination with antibiotics	Vidya et al. (2016)
Multidrug resistant	*E. coli, S. aureus, Salmonella typhimurium*	Depend on coexisting chemicals that were not removed from AuNPs	Zhang et al. (2015, Dasari et al. (2015)
Multidrug resistant	*E. coli*	Interaction between lysozyme micro-bubbles and cell wall	Mahalingam et al. (2015)
Multidrug resistant	*S. aureus, E. coli, P. aeruginosa*	Disruption of bacterial cell wall	Li et al. (2014), Yang et al. (2017)
Multidrug resistant	*E. coli, S. aureus*	Interaction with biomolecules	Kim et al. (2017)
Multidrug resistant	*E. coli*, *K. pneumoniae*, *E. cloacae*	Photodynamic therapy/ photothermal therapy; Photodynamic therapy/ photothermal therapy	Khan et al. (2017)
Multidrug resistant	*S. aureus, E. coli, E. cloacae, P. aeruginosa*	Photodynamic therapy/ photothermal therapy	Mocan et al. (2016)
Multidrug resistant	*Salmonella typhimurium*	Photodynamic therapy/ photothermal therapy	Lin and Hamme II (2015)
Multidrug resistant	*S. aureus*	Photodynamic therapy/ photothermal therapy	Gil-Tomás et al. (2007)
Multidrug resistant	*E. coli*	ROS generation	Zhang et al. (2013)
Multidrug resistant	*E. coli*	Change of membrane potential and inhibition of ATP synthase; inhibition of the subunit of the ribosome for tRNA binding	Cui et al. (2012)
Multidrug resistant	*E. coli*, *K. pneumoniae*, *S. aureus*, *B. subtilis*	Change of membrane potential and inhibition of ATP synthase; inhibition of the subunit of the ribosome for tRNA binding	Shamaila et al. (2016)

(continued)

Table 9.3 (continued)

Type of antibiotic resistance	Targeted bacteria	Mechanisms of antibacterial activity of AuNPs	Ref.
Multidrug resistant	*S. aureus*	Photoacoustic detection and photothermal therapy	Galanzha et al. (2012)
Multidrug resistant	*E. coli, K. pneumoniae*	Not revealed	Bresee et al. (2014)
Multidrug resistant /biofilm formation	*P. aeruginosa*	Conjugation with AMP	Casciaro et al. (2017)
Multidrug resistant/ biofilm formation	*Staphylococci, Enterococci,* and other bacterial strain	Conjugation with AMP	Kuo et al. (2016)
Multidrug resistant /biofilm formation	*E. coli, S. aureus, K. pneumoniae, P. aeruginosa*	Conjugation with AMP	Rai et al. (2017)
Multidrug resistant /biofilm formation	*Salmonella typhimurium*	Conjugation with AMP	Yeom et al. (2016)

9.4 Mechanism of Antibacterial Activity of Au Nanoparticles

Drug-resistant bacteria acquire genetic modification to exclude antimicrobial drugs and become less sensitive to drugs. To find an effective way to control the threat of bacterial drug resistance, a novel approach to enhance antimicrobial activity is urgently needed. AuNPs are the most studied metal nanoparticles (NPs) for antibacterial applications (Borzenkov et al. 2020). They are biologically inert and pure form of Au does not exert any antibacterial activity (Zhang et al. 2015). However, the surface area of AuNPs is suitable for conjugation with antibiotics and other drugs. A wide range of proteins, drugs, and even nucleotides have also been successfully delivered using AuNPs in the recent past (Perzanowska et al. 2021). Though the exact mechanism underlying the antimicrobial propensity of AuNPs remains unclear, several factors including size, shape, and surface functionalization significantly influence the activity of AuNP.

Major pathways through which AuNPs exert antimicrobial activity include (i) direct contact with bacteria (Shaikh et al. 2019), (ii) physical disruption of membrane (Piktel et al. 2021), (iii) generation of reactive oxygen species (ROS) (Yu et al. 2020), (iv) interaction with cellular proteins and genetic elements (Wang et al. 2015), and (v) trigger host-response immunity (Dykman and Khlebtsov 2017) (Fig. 9.2a). The antimicrobial efficacy of AuNP is largely dependent on their size and shape. The size of the AuNPs plays a critical role in their bactericidal activity, and functionalization with hydrophilic molecule enhances their interaction with bacterial membrane. Hayden et al. reported the size-dependent antimicrobial effect

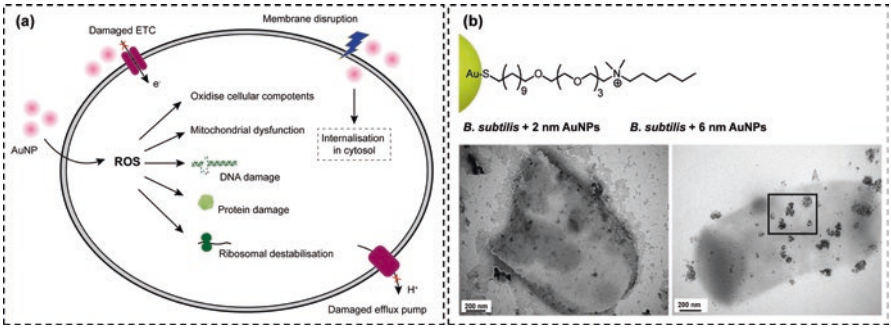

Fig. 9.2 Mechanism of antibacterial activity of AuNPs. (**a**) AuNPs cause irreversible membrane damage and, hence, particles get internalized in the cytosol. AuNPs then interfere with the cellular components and induce the generation of reactive oxygen species (ROS). ROS brings about different kinds of damage and finally promotes cells to apoptosis. Damaged electron transport chain (ETC) and efflux pump change the electron and proton homeostasis in a cell, respectively. (**b**) Size-dependent antimicrobial activity of gold (Au) NPs. TEM images confirmed *B. subtilis* membrane rupture by 2 nm AuNPs but not in case of 6 nm NPs. (Reproduced from Hayden et al. (2012) with permission. Copyright © 2012 American Chemical Society)

of cationic AuNPs (Hayden et al. 2012) (Fig. 9.2b). The larger particles (>100 nm) are unable to cross the bacterial membrane; however, smaller particles do and make pores in the membrane (Zheng et al. 2017; Xing et al. 2018).

The large surface area of AuNPs allows the attachment of a wide range of functional elements to enhance the pristine antimicrobial effect. Hence, both AuNPs and their functionalized derivatives have been used to control infections caused by antimicrobial-resistant (AMR) pathogens (Li et al. 2014; Zhao et al. 2013). In addition to increased bactericidal effect, functionalization of the AuNPs' surface also stabilizes the particle and provides prolonged effective and safe drug delivery (Tao 2018). Multivalent Au atom is conjugated with multiple ligands to enhance its antimicrobial activity (Zheng et al. 2017; Ortiz-Benítez et al. 2019). In addition, capping agents used in the synthesis of AuNPs also disrupt cell membrane via electrostatic interactions. AuNPs capped with a mixture of different small molecules can also enhance their antibacterial propensity. For example, AuNPs of 2 nm size capped with p-mercaptobenzoic acid (pMBA-Au) are not effective against bacteria. When pMBAs on the AuNPs' surface are partially replaced with a mixture of 2-mercaptoethylamine and 3-mercaptopropylsulfonate, the resultant AuNPs show 99.9% growth inhibition against *E. coli* at 0.5 mM concentration (Bresee et al. 2011). Li et al. systematically modified the surface of AuNPs to combat multidrug-resistant (MDR) bacteria. Herein, they functionalized 2 nm size AuNPs using hydrophobic molecules having different chain length (Li et al. 2014). The hydrophobic interaction destroys the integrity of bacterial membrane and allows internalization of metal ions, loaded drugs, and protein inhibitors. On the contrary, it also allows the leakage of cytoplasmic content.

The interaction between cationic AuNPs and negatively charged membrane proteins (mostly teichoic acids) results in the aggregation, protrusion and, therefore,

damage the membrane permanently (Hayden et al. 2012; Zhao et al. 2010). The positive charge of AuNPs is responsible for better interaction with negatively charged bacteria which leads to membrane rupture. However, it has been reported that interaction of AuNPs with bacteria changes the membrane permeability, interrupts the electrolyte balance, and deactivates protein function (Wang et al. 2017b). Payne et al. confirmed that the membrane-attached AuNPs penetrate the cell wall of bacteria using small-angle X-ray scattering (Payne et al. 2016). This phenomenon resulted in the disruption of cytosolic environment and leakage of cellular components (Fig. 9.3).

Ortiz-Benítez et al. found that AuNPs reached the cytosolic environment of resistant *S. pneumoniae* and formed spherical cytoplasmic structures known as inclusion bodies (Ortiz-Benítez et al. 2019). They separated the proteins from the inclusion bodies that are potential candidates to facilitate the uptake of NPs in *S. pneumoniae*.

However, conjugation of antibiotics to AuNPs provides enhanced bactericidal effect than pristine AuNPs (Rattanata et al. 2016). Bagga et al. reported that AuNPs-levofloxacin showed greater bactericidal effect against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa* (Payne et al. 2016; Bagga et al. 2017). XX et al. reported a one-pot, fast synthesis of vancomycin-conjugated AuNP which had 16-fold better antibacterial activity against vancomycin-resistant *Enterococci* when compared to free vancomycin (Wang et al. 2018). Other similar

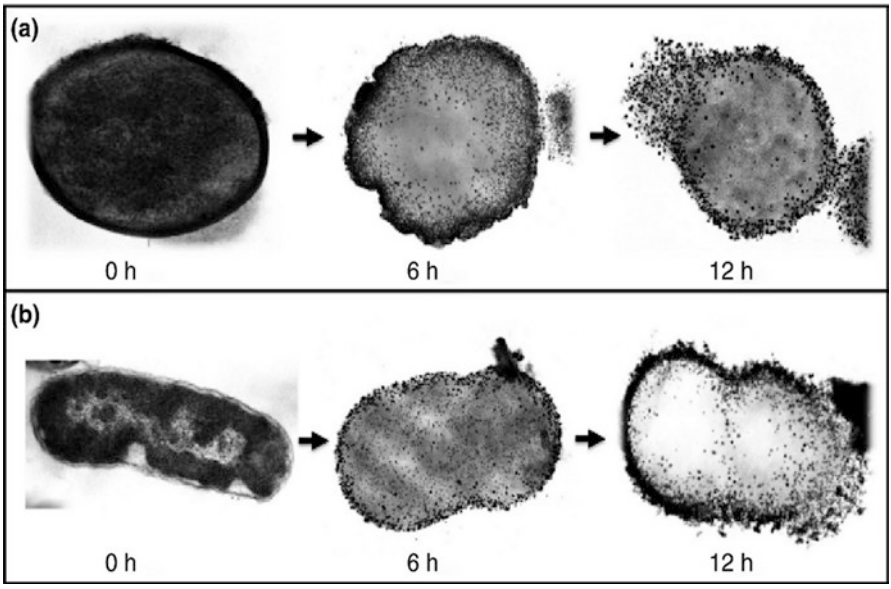

Fig. 9.3 Transmission electron microscopic images of bacteria. Sequential images of gram-positive *Staphylococcus epidermidis* bacteria (**a**) and gram-negative *Enterobacter aerogenes* bacteria (**b**) treated with kanamycin-AuNPs after 0, 6, and 12 h of incubation. (Reproduced with permission Payne et al. (2016). Copyright © 2016)

studies also support the codelivery of antibiotics with AuNP to reduce resistance development (Fuller et al. 2020; Justo and Bosso 2015; Sans-Serramitjana et al. 2016; Wang et al. 2020; Fan et al. 2019). Thus, the delivery of antibiotic-conjugated AuNPs not only improve antibacterial efficacy but also require low dose of free antibiotic. Moreover, they also retard bacteria from developing resistance to antibiotics (Chopra 2007). Antibiotic-conjugated AuNPs exert higher antibacterial activity with minimal toxicity (Huh and Kwon 2011). Though synergistic effect of AuNPs-drug conjugate is always discussed as responsible for enhanced antimicrobial activity, the exact mechanism is still unknown. It is hypothesized that this stable conjugation improves internalization of antibiotics to resistant cells (Gu et al. 2003). Only a stable conjugation offers better antibacterial effect. Major drawbacks of antibiotic adsorption on AuNPs include aggregation and poor dispersity of the nanoparticles leading to compound instability. On the other hand, the conjugation of amphiphilic antimicrobial peptides (AMPs) with AuNPs enhances the antibacterial activity of nanoparticles. The advantage of conjugating amphiphilic AMPs is that they facilitate the interaction of AMP-AuNP with bacterial membrane (Wimley and Hristova 2011; Craik et al. 2013; Wadhwani et al. 2017). For example, Lee et al. conjugated hexahistidine-tagged AMPs with aptamer-bound AuNP (Lee et al. 2017). The resultant conjugate was highly effective against infectious pathogens including *Vibrio vulnificus*.

The photothermal property of AuNPs is advantageous for their biomedical applications (Mahmoud et al. 2019). AuNPs produce heat upon illumination with laser, and the thermal energy damages the neighboring bacteria. It is important to make sure that the AuNPs and bacteria are in close proximity so that the photothermal energy generated in the local environment damages the target cell (Mahmoud et al. 2018). Photothermal therapy (PTT) and photodynamic therapy (PDT) are the two main approaches followed by AuNPs to kill bacteria upon laser irradiation. In case of PTT, AuNPs convert the light energy into heat and enhances local temperature to kill bacteria (Jo and Kim 2013; Zhu et al. 2014; Pallavicini et al. 2017). On the other hand, PDT relies on the irradiation of photosensitizers to generate more reactive oxygen species (ROS) that kill bacteria (Venditti 2019). TEM images confirmed the laser-induced bacterial death after treatment with AuNPs. Bermúdez-Jiménez et al. reported the antibacterial effect of chitosan hydrogel–embedded AuNPs against clinical MDR pathogens upon illumination with laser (Bermúdez-Jiménez et al. 2019) and the minimum inhibitory concentration (MIC) was <4 μg/ml. The low-power infrared diode laser ruptured the bacterial membrane through enhanced ROS production. The principle of PDT is to generate toxic singlet oxygen upon illumination of photosensitizers with visible light. The highly reactive singlet oxygen damages the neighboring bacterial membrane, interferes with the cellular metabolic pathways, and damages the DNA (Bertoloni et al. 2000; Narband et al. 2009). In recent studies, photosensitizer-embedded AuNPs showed effective antimicrobial activity against both gram-positive and gram-negative bacterial strains (Rossi et al. 2019; Jain et al. 2006; Pallares et al. 2016; Darby et al. 2016; Ni et al. 2008). PDT

is very safe and effective; however, it is highly recommended to deliver therapeutic concentration of the photosensitizers.

Cui et al. investigated the molecular mechanism of bactericidal activity of AuNPs using transcriptomic and proteomic approaches. Two major ways of exerting antibacterial activities include decrease in the cellular ATP level that collapses the membrane potential and the inhibition of tRNA-binding ribosomal protein subunit (Cui et al. 2012). Thus, AuNPs interfere with the activities of ATPase and tRNA. Hence, decoding of mRNA responsible for functional protein enhances ROS-mediated chemotaxis in bacteria and leads to apoptosis (Cui et al. 2012). The most supported mechanism for antibacterial activity of the AuNP is the generation of reactive oxygen species (ROS). These highly reactive chemicals enhance oxidative stress and form vacuoles inside cells (Mohamed et al. 2017).

It is important to highlight that commercially available antibiotics do not follow the multidimensional mode of action like AuNPs to inhibit bacterial growth. Hence, AuNPs can be a good alternative tool to control MDR pathogens. The different mode of antibacterial action of AuNPs is due to the structural differences of gram-positive and gram-negative bacteria (Ranjan Sarker et al. 2019). Hence, AuNPs have a promising future in the field of drug-delivery system (DDS) because delivery of drugs using AuNP is not only effective but also less toxic.

In-depth studies are recommended to unravel the precise mode of action involved in AuNPs-bacteria interaction and their inhibition.

9.5 Biocompatibility of Au Nanoparticles

The field of nanomaterials is expanding rapidly with a wide range of applications (Khan et al. 2019). Besides having several medical applications, AuNPs have toxicities associated with them. Hence, it is very important to know the basic information about the nanomaterials, especially composition, variability of size, shape, surface charge, surface area, surrounding media, and aggregation tendency in biological fluid that influence the biocompatibility of NPs. In this section, properties of Au NPs will be discussed to understand their biocompatibility cell.

A range of techniques have been used to investigate the biocompatibility of AuNPs (Fig. 9.4). Table 9.4 summarizes the principle and benefits of each assay. MTT assay is considered as the "gold standard" to investigate the toxicity of AuNPs. It is a colorimetric assay to determine cellular metabolic activity (Stockert et al. 2018). Herein, enzymatic activity of mitochondrial reductase is monitored under a defined condition. In an oxidation reaction, the enzyme reduces a yellow-colored tetrazolium dye (known as MTT or 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyltetrazolium bromide) and produces insoluble purple-colored formazan. This irreversible reaction reflects the number of live cells at different time points.

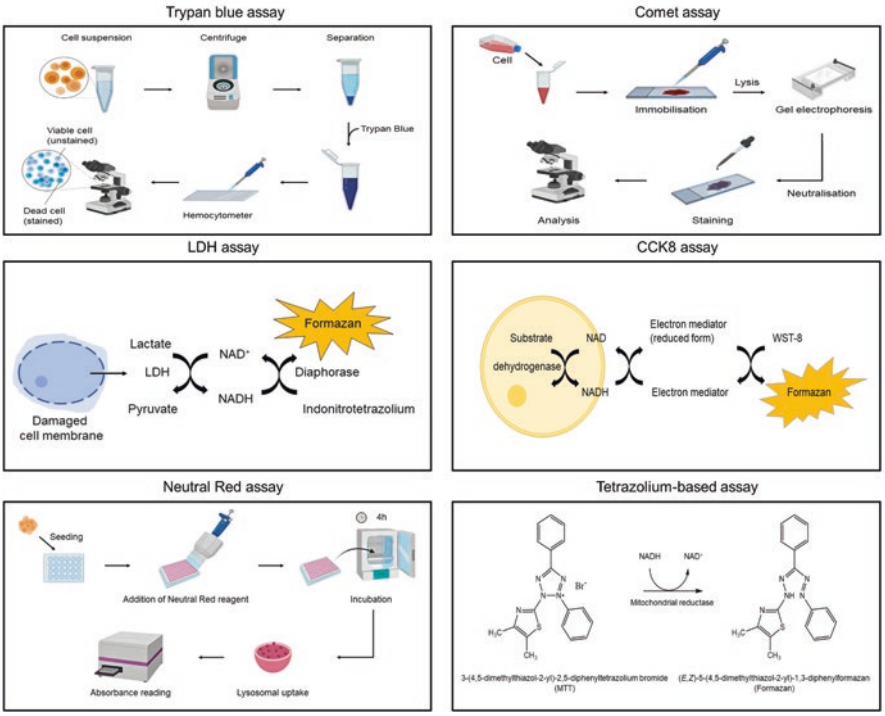

Fig. 9.4 Commonly used assays to determine cell viability

Cell number is quantified by measuring the absorbance of formazan at 570 nm. The degree of formazan production reflects the number of dead cells and is directly proportional to light absorption.

One of the pioneering reports on the biocompatibility assessment of AuNPs was reported by Shukla et al., where the biocompatibility and the uptake of AuNPs by RAW 264.7 macrophage cells were investigated (Shukla et al. 2005). Their findings suggest that AuNPs are highly biocompatible having antioxidation potential at higher doses besides suitable for prolonged treatment. In addition, they found that spherical AuNPs did not induce the secretion of proinflammatory cytokines (e.g., TNFα and interleukin β) by macrophage cells. Chithrani et al. studied the effect of AuNP's shape, size, and toxicity (Chithrani et al. 2006). They concluded that citrate-capped spherical and rod-shaped AuNPs did not cause any significant toxicity to HeLa cells. This study was followed by other research groups and found negligible toxicity for spherical and rod-shaped AuNPs using different cell lines in vitro (Khan et al. 2007; Gu et al. 2009; Villiers et al. 2010). We demonstrated that functionalization of elongated tetrahexahedral (ETHH) AuNPs with α-lipoic

Table 9.4 Summary of commonly used assays to evaluate the cytotoxicity of AuNPs

Assay	Principle	Remarks	Reference
Trypan blue assay	This diazo dye penetrates the cell membrane of dead cells and stains them selectively	Identifies live (unstained) and dead (blue) cells Provides quantitative cell-to-cell count Fast method Long-time incubation may give false positive result	Strober (2001)
Comet assay	Denatured cleaved DNA fragments migrate out of the cell under electrophoresis and the undamaged DNA remains within the cell membrane	Single-cell gel electrophoresis Economical Sensitive method	Fairbairn et al. (1995)
LDH assay	Colorimetric detection of lactate dehydrogenase (LDH)	Depends on LDH detection Qualitative and quantitative cell count Not preferable for multiple samples	Kumar et al. (2018)
Cell Counting Kit 8 (CCK8)	Cellular dehydrogenases cause reduction of water-soluble tetrazolium salt, WST-8 [2-(2-methoxy-4-nitrophenyl)-3-(4-nitrophenyl)-5-(2,4-disulfophenyl)-2H-tetrazolium, monosodium salt] And produce orange colored formazan	Colorimetric assay No premixing is required Rapid and sensitive Expensive Absorbance interference	Cai et al. (2019)
Neutral Red assay	Incorporation of dye lower in dead cell	Depends on lysosomal function Simple and fast method Quantitative cell count	Repetto et al. (2008)
Tetrazolium-based assays	Conversion of tetrazolium dye to insoluble formazan	Depends on mitochrondiral function Colorimetric assay Simple and fast method Qualitative and quantitative cell count Repeatable Economical Not suitable for suspending cells Seeding amount and assay duration must be optimized	Stockert et al. (2018), Vistica et al. (1991)

acid, a natural antioxidant, increased their hemocompatibility as well as biocompatibility to human red blood cells (RBCs) and HeLa cells, respectively (Ranjan Sarker et al. 2019). Recently, we also reported that functionalization of concave cube AuNPs (CCAu) with α-lipoic acid and glutathione, a tripeptide with antioxidation potential, increased their hemocompatibility to human RBCs and biocompatibility to HeLa cells, L929 fibroblasts, and CHO-GFP cells (Pandala et al. 2021). On the contrary, Patra et al. synthesized spherical (33 nm in diameter) AuNPs and investigated their toxicity using three different cell lines (Patra et al. 2007). They found the particles were toxic to human lung carcinoma cells (A549), but compatible with baby hamster kidney cells (BHK21) and human liver carcinoma cells (HepG2).

The hydrodynamic size of AuNPs plays an important role in terms of their cellular uptake and biocompatibility. Earlier studies found that size variability of AuNPs demonstrates negligible toxicity (Khan et al. 2007; Gu et al. 2009; Villiers et al. 2010; Connor et al. 2005). Large AuNPs are generally stable, inactive, noncatalytic, and biocompatible (Khlebtsov and Dykman 2011). Sophisticated tools including inductively coupled plasma mass spectrometry (ICP-MS) are used to quantify AuNPs taken up inside cell (Merrifield et al. 2018). Moreover, electron microscopy confirmed the presence of Au particles in the treated cells (Shukla et al. 2005; García et al. 2013). Chithrani et al. and others studied the cellular uptake of a wide range of AuNPs and quantified the number of nanoparticles inside each cell using inductively coupled plasma atomic emission spectroscopy (Chithrani et al. 2006; Osaki et al. 2004; Huo et al. 2013; Wang et al. 2010; Heuskin et al. 2017). All these studies reported that the maximum uptake was observed in case of 50 nm AuNPs without any cytotoxic effect. Karakoçak et al. used two independent methods (i.e., electric cell-substrate impedance sensing and MTT assay) to investigate the cellular uptake and biocompatibility of spherical, rod-, and cube-shaped AuNPs (Karakoçak et al. 2016). They concluded that sphere-shaped AuNPs have better biocompatibility when compared to Au rods (Fig. 9.5). However, cube-shaped AuNPs neither entered into cells nor had any cytotoxic effect.

Most often rod-shaped AuNPs are synthesized using a cationic surfactant called CTAB. Wang et al. found that free CTAB up to 1 μM is toxic to mammalian cells (Wang et al. 2008). Therefore, several strategies including chemical exchange or surface functionalization have been chosen to make Au nanorods less toxic. Polyethylene glycol (PEG), a hydrophilic polymer, has been widely used to modify AuNPs' surface. However, PEGylation of AuNPs interferes with the cellular uptake process through reduced endocytosis (Nel et al. 2009; Doak et al. 2009). Chen et al. evaluated intraperitoneally injected eight AuNPs of different size (3–100 nm) and found size dependent toxicity in mice (Chen et al. 2009).

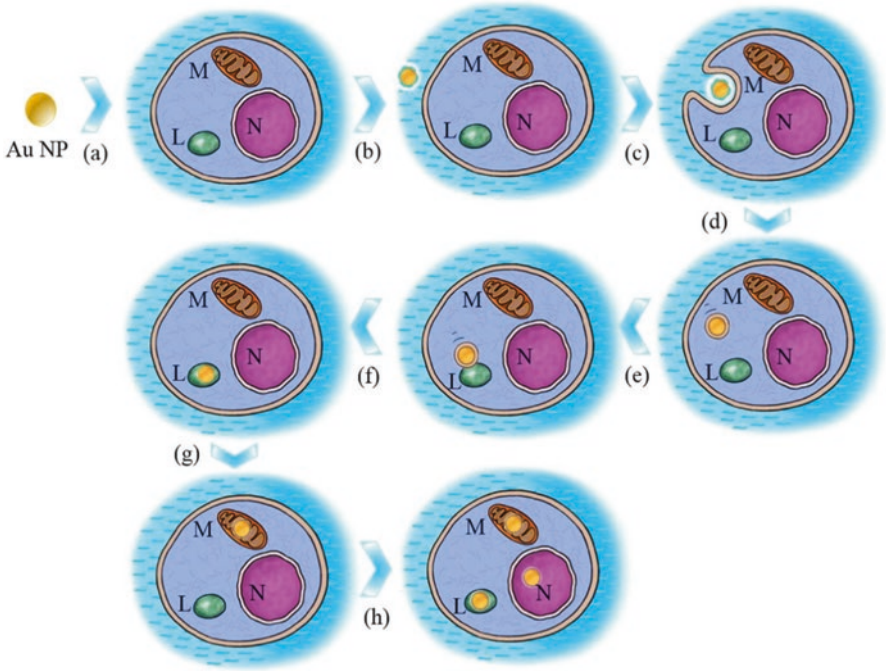

Fig. 9.5 The mechanism of AuNPs-mediated cytotoxicity. (**a**) Exposure of AuNPs to ARPE-19 cell. (**b**) Dynamic bipolymer layer (thick and loose blue color coating) creates a superficial surface exposed to the cell membrane. (**c**,**d**) Uptake of AuNPs by endocytosis. (**e**) Fusion of endocytic vesicle with lysosome. (**f**) Complete internalization of AuNPs by lysosome. (**g**) AuNPs cross the single membrane of lysosome and penetrate the mitochondrial intermembrane space to initiate apoptosis signal. (**h**) AuNPs available in the cytoplasm cause cell death by activating subcellular signaling pathways for apoptosis, initiating cell shrinkage, decreasing cytoplasmic shrinkage, and beginning subcellular fragmentation. Here, L lysosome; M mitochondria; and N nucleus. (Reproduced with permission Karakoçak et al. (2016) Copyright © 2016 Elsevier Ltd.)

9.6 Conclusions and Future Perspectives

Multidrug-resistance bacteria are exerting real threat to the existence of mankind because they have become resistant to almost all the commercially available antibiotics. Overuse and misuse of antibiotics are the main causes of the development of bacterial resistance mechanisms against antibiotics. Gold nanoparticles demonstrate antibacterial activity mainly through the oxidation of bacterial membrane resulting in the formation of pores on the membranes. As a result, AuNPs interact with the cellular DNA, proteins, and other macromolecules and cause bacterial death. Since AuNPs demonstrate antibacterial activity by damaging bacterial membrane and other subcellular organelles, they demonstrate antibacterial activity against a wide range of bacteria including pathogenic bacteria and multidrug-resistant bacteria. Furthermore, AuNPs are highly biocompatible in terms of their

compatibility with various cell lines, red blood cells (RBCs), and mouse model (i.e., in vivo). Hence, in clinical trials, AuNPs can be recommended to be used as an alternative nanoweapon to commercially available antibiotics to tackle multidrug-resistant bacteria.

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