Chapter 14
Biosynthesis, Mechanisms, and Biomedical Applications of Silver Nanoparticles

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Abstract Nanoparticles (NPs) can be developed to improve drug penetration and reorient chemotherapy, or selectively target the cancer cells or cell compartment. Both passive and active targeting strategies are used to redirect the anticancer drugs. Noble metals such as the silver NPs (AgNPs) are characterized by electrical, optical, and thermal properties, and can be integrated into products for optical, biological and chemical sensor applications such as pastes, conductive inks, and fillers for high stabilization, electrical conductivity, and low sintering temperatures. The biosynthesis of AgNPs, making use of bacteria, fungi, actinomycetes, yeast, algae, and plants, is eco-friendly, green, nontoxic and inexpensive. The AgNPs sytnhesized are of various shapes and sizes. The AgNPs have diverse bioactivities including antibacterial, antifungal, antiviral, anti-inflammatory, anti-angiogenic, and anticancer activities, with great potential for use in cancer diagnosis and therapy. The mechanisms of AgNP-induced cytotoxicity include endoplasmic reticulum stress, lactate dehydrogenase leakage, and enhanced reactive oxygen species level. Co-application of AgNPs and natural products could play an essential role in nanoscience and nanotechnology, especially in nanomedicine for cancer diagnosis and therapeutics.

Keywords Anti-cancer · Nanobiotechnology · Nanocarrier · Nanomedicine · Silver Nanoparticles

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14.1 Introduction

Nanoparticles (NPs) and nanomaterials can be utilized for human medical applications, including for the delivery of therapeutic drugs to cells, or for the imaging of tissues and organs. NPs are divided into organic and inorganic materials. Organic NPs include the carbon NPs (fullerenes) and inorganic NPs include the magnetic, noble metals (such as gold and silver) and semi-conductive (such as titanium dioxide and zinc oxide) NPs. The inorganic NPs have superior material features with functional versatility and have potential for application in imaging tools as well as for disease treatment owing to their sizes and their benefits as pharmaceutical agents and chemotherapy drugs. Mesoporous silica is established along with the molecular machinery to be used for imaging and as release systems. NPs have been used successfully for the delivery of therapeutic agents (Zhang et al. 2008), in diagnostics for chronic diseases (Hong et al. 2008), and the treatment of bacterial skin infections and burn wounds (Rai et al. 2009). Gold NPs are widely used in imaging, as drug carriers, and in the thermal treatment of biological targets (Cheon and Underwood 2009). The bactericidal behavior of NPs is attributed to the presence of electronic effects as a result of changes in the local electronic structure of the surface owing to their smaller sizes. The NPs become attached to the cell membrane and penetrate inside the bacteria.

Several NPs that are loaded with drugs interact with the organs and tissues and are eventually taken up by the cells. The tissue, cell and cell organelle distribution of the drugs can therefore be controlled and improved by entrapping them into the colloidal NPs, such as the nanocontainer or nanocarrier (Minchinton and Tannock 2006; De Jong and Borm 2008; Zhang et al. 2013). However, not all nanocarriers penetrate tumor tissue (Lammers et al. 2012). Nanomedicine compounds can be designed to improve drug penetration and reorient the chemotherapy or target the cancer cells or cell compartment with the compounds selectively. Both negative and effective targeting strategies are used to redirect the anticancer drugs (Wicki et al. 2015). The nanomedicine treatments can increase the circulatory time of the compound and mediate the release of stimulant-responsive drugs as well as the absorption of the stimulant medication. This may result in reduced tumor cell resistance against targeted NPs (Huwyler et al. 2002; Hu and Zhang 2009). NP drug delivery systems have great advantages such as delivery through the smallest capillary vessels owing to their small sizes and avoiding fast clearance by phagocytes, infiltration of the cells and tissue gap to reach the target site. Existing controlled release features such as the pH, ion, and/or temperature sensitivity of the substance can improve the efficacy of the drugs, whilst minimizing the toxic side effects (Zhang et al. 2010a, b).

Nanobiotechnology combines the nanotechnology area with microbiology, chemistry and physical sciences, and the synthesis of NPs by utilizing the biological systems such as plants, bacteria, and fungi (Ahmad et al. 2003; Prasad 2014; Prasad

et al. 2016, 2018). NPs exhibit new or improved properties based on the specific characteristics such as size, distribution, and morphology, resulting in rapid and tunable applications of the NPs and nanomaterials (Dakhil 2017). The common methods for the synthesis of NPs include physical and chemical approaches using laser ablation, pyrolysis, lithography, chemical vapor deposition, sol-gel techniques, and electro-deposition, but these are expensive and hazardous (Vijayakumar et al. 2013). Different reactants are used, especially reducing agents such as sodium borohydride (Kim et al. 2007), potassium bitartrate (Tan et al. 2003), methoxypolyethylene glycol (Zewde et al. 2016), and hydrazine (Li et al. 1999). It also requires a stabilizing agent such as sodium dodecyl benzyl sulfate or polyvinyl pyrrolidone to prevent the agglomeration of metallic NPs. Generally, the chemical methods are low-cost for high volume, but may involve contamination from the precursor chemicals, the use of toxic solvents, and the generation of hazardous by-products (Thakkar et al. 2010).

There is an increasing need to develop simple, cost-effective, high-yield, and eco-friendly procedures (Gurunathan et al. 2013a, b). The alternative green method for the biosynthesis of metal NPs is via the living organisms or material of biological origin. NPs can be synthesized by using living bacteria or fungi, or plant extracts, which is environmentally friendly, takes place around room temperature or lower, and requires little intervention or input of energy (Dash 2013). The important three factors are: (a) the solvent, (b) the reducing agent, and (c) the nontoxic material. The availability of amino acids, proteins, or secondary metabolites could facilitate the synthesis process, prevent particle aggregation, and is pollution-free. The biological methods using bacterial protein or plant extracts as reducing agents allow control of the particle size, shape, and monodispersity of the NPs, which are important for various biomedical applications (Gurunathan et al. 2009, 2014). The availability of a vast array of biological resources, a decreased time requirement, high density, stability, and the ready solubility of the prepared NPs in water (Thakkar et al. 2010), confer major advantages over the chemical synthetic route of other metallic-based anticancer agents (Caroling et al. 2013; Chaudhari et al. 2012; Yazdi et al. 2015; Jaffat et al. 2017). Many microbes, both unicellular and multicellular, produce inorganic materials, either intra- or extracellularly. Bacteria, yeast, and fungi play important roles in the remediation of toxic metals through the reduction of metal ions and act as nanofactories (Prasad et al. 2016). These microbes are extremely good candidates in the synthesis of cadmium, gold, and silver nanoparticles (AgNPs; Table 14.1) (Jeevan et al. 2012). Extracellular synthesis of NPs occurs outside the bacterial cell. These NPs, spherical, disk, cuboidal, hexagonal, or triangular shaped, have been synthesized using cells, culture supernatant, or aqueous cell-free extract (Klaus et al. 1999; Srivastava and Constanti 2012; Oves et al. 2013; Singh et al. 2013). The NPs are collected as pellets, which can be dissolved in suitable solvent. The extracellular methods are more useful than the intracellular methods because of the ease of obtaining the NPs from the solution (Singh and Shedbalkar 2015).

Table 14.1 Biosynthesis of silver nanoparticles (AgNPs) from different bacterial species

Bacteria species	Shape	Size (nm)	Biosynthesis	Activities	References
Gram-negative					
Acinetobacter calcoaceticus	Spherical	8–12	Extracellular	Enhanced antibacterial activity	Singh et al. (2013)
		4–40	Extracellular	Antibacterial	Gaidhani et al. (2013)
Aeromonas sp. SHlO	–	6.4	Extracellular and intracellular	–	Mouxhg et al. (2006)
Bordetella sp.	–	63–90	Extracellular	Antibacterial	Thomas et al. (2012)
Enterobacter aerogenes	Spherical	25–35	Extracellular	–	Karthik and Radha (2012)
Escherichia coli	Spherical	42.2–89.6	Extracellular	–	Gurunathan et al. (2009)
Escherichia fergusonii	Spherical	10–50	Extracellular	Cytotoxicity against MCF-7 cells	Gurunathan et al. (2013a, 2013b)
Geobacter sulfurreducens	–	–	Extracellular	–	Law et al. (2008)
Gluconobacter roseus	–	10	Extracellular	Cytotoxic effects on platelets	Krishnaraj and Berchmans (2013)
Idiomarina sp. PR58-8	–	25	Intracellular	–	Seshadri et al. (2012)
Klebsiella pneumoniae	Spherical	15–37	Extracellular	Antibacterial	Kalpana and Lee (2013)
	–	5–32	Extracellular	Enhanced antibacterial activity	Shahverdi et al. (2007)
Morganella spp.	Quasi-spherical	10–40	Extracellular	–	Parikh et al. (2011)
Morganella psychrotolerans	Spherical	70–100	Extracellular	–	Ramanathan et al. (2011)
Proteus mirabilis	Spherical	10–20	Extracellular and intracellular	–	Samadi et al. (2009)
Pseudomonas aeruginosa	Spherical, disk-shaped	6.3 ± 4.9	Extracellular	–	Kumar and Mamidyala (2011)
	Quasi-spherical	5–25	Intracellular	–	
Pseudomonas stutzeri AG259	Triangular, hexagonal, and spheroidal	200	Cell poles	–	Klaus et al. (1999)

Rhodobacter sphaeroides	Spherical	3–15	Extracellular	–	Bai et al. (2011)
Shewanella oneidensis MR-1	Spherical	2–16	Extracellular	–	Debabov et al. (2013)
Stenotrophomonas maltophilia	Cuboidal	93	Extracellular	Antimicrobial and anti-cancer	Oves et al. (2013)
Vibrio alginolyticus	Spherical	50–100	Extracellular and intracellular	–	Rajeshkumar et al. (2013)
Xanthomonas oryzae pv. *oryzae* BXO8	Spherical, triangular, rod-shaped	14.86	Extracellular	–	Narayanan and Sakthivel (2013)
Gram positive					
Bacillus sp.	–	5–15	Extracellular and periplasmic	–	Pugazhenthiran et al. (2009)
Bacillus subtilis	Triangular, hexagonal	–	Extracellular	–	Kannan et al. (2011)
Bacillus subtilis	Spherical	20–60	Intracellular	Antifungal activity	Paulkumar et al. (2013)
Bacillus thuringiensis	–	43.52–142.97	Extracellular	Larvicidal activity against *Aedes aegypti*	Banu et al. (2014)
	Spherical	–	intracellular	Antimicrobial	Dash (2013)
Brevibacterium casei	Spherical	10–50	Intracellular	Anti-coagulant effect	Kalishwaralal et al. (2010)
Corynebacterium SH09	–	10–15	Extracellular	–	Zhang et al. (2005)
Staphylococcus aureus	–	160–180	Extracellular	Antibacterial	Nanda and Saravanan (2009)
Exiguobacterium sp. KNU1	Spherical	5–50	Extracellular	Antibacterial	Tamboli and Lee (2013)
Geobacillus stearothermophilus	Spherical	5–35	Extracellular	–	Fayaz et al. (2011)
Lactobacillus mindensis	Spherical	2–20	Extracellular	–	Dhoondia and Chakraborty (2012)
Lactobacillus mixture	Spherical	30–100	Extracellular	Antioxidant	Dakhil (2017)
Lactobacillus acidophilus 58p	Spherical	30.65 ± 5.81	Extracellular	Antimicrobial	Garmasheva et al. (2016)
Lactobacillus plantarum 92 T	Spherical	19.92 ± 3.4	Extracellular	Antimicrobial	
Pediococcus pentosaceus	–	–	Intracellular	–	Sintubin et al. (2009)
Rhodococcus NCIM 2891	Spherical	30	Extracellular	–	Otari et al. (2014)

14.2 Silver Nanoparticles

Silver nanoparticles (AgNPs) are important because of their unique properties (Klaus-Joerger et al. 2001). AgNPs have gained special interest over gold and copper NPs because of their surface plasmon resonance (SPR) energy, which is located away from the interband transition energy (El-sheekh and El-kassas 2016). Because of their catalytic, optical, electrical, and magnetic properties, AgNPs have applications in electronic components, biosensors, environmental remediation, antimicrobial and anticancer agents, cosmetic products, optical catalysis, drug delivery (Klaus-Joerger et al. 2001; Kasthuri et al. 2009; Dubey et al. 2010; Nabikhan et al. 2010; Nithya and Ragunathan 2012; Aziz et al. 2014, 2015, 2016, 2019; Hussein et al. 2020), spectrally selected coatings for solar energy absorption, intercalation material for electrical batteries, optical receptors, chemical catalysis, and bio-labeling (Kalimuthu et al. 2008). AgNPs have been used extensively in household utensils, health care industry, and in food storage, environmental, and biomedical applications such as antibacterial, antifungal, antiviral, anti-inflammatory, anticancer, and anti-angiogenic products (Fig. 14.1) (Zhang et al. 2016). The AgNPs-based products have been approved by a range of accredited bodies, including the US FDA, US EPA, SIAA of Japan, Korea's Testing and Research Institute for the Chemical Industry, and the FITI Testing and Research Institute (Abou El-Nour et al. 2010).

14.2.1 Biosynthesis

Silver nanoparticles have been biosynthesized using methods including the chemical reduction of silver (Ag) ion in aqueous solution (Liz-Marzán and Lado-Touriño 1996), photo-reduction (Pileni 2000; Sun et al. 2001), thermal decomposition in organic solutions (Esumi et al. 1990), and laser radiation (Henglein 1993, 1998). However, these are expensive, unstable, and also the AgNPs are toxic and cause

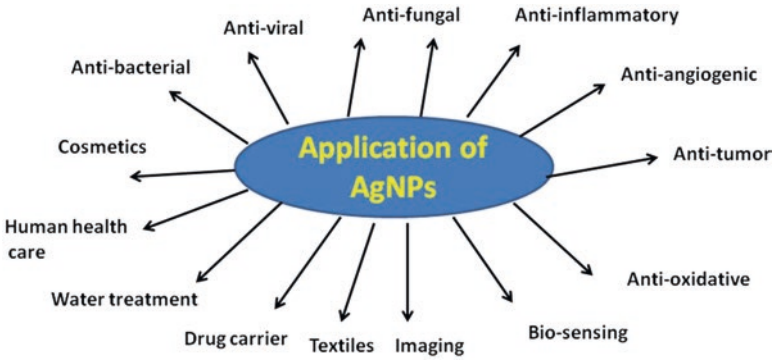

Fig. 14.1 Applications of silver nanoparticles (AgNPs) (Adapted from Zhang et al. 2016)

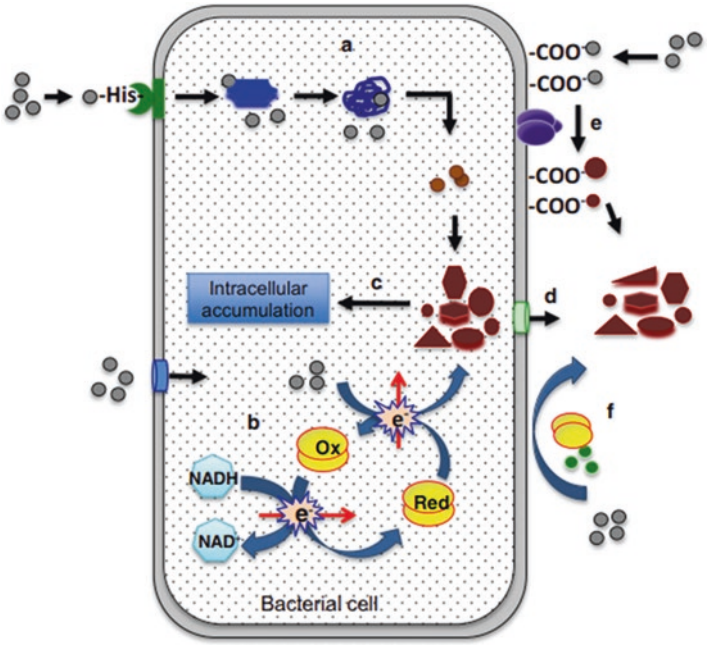

Fig. 14.2 Proposed mechanism of AgNP synthesis (Adapted from Singh and Shedbalkar 2015). (**a**) Cellular uptake of silver ions and activation of silver reduction machinery, (**b**) electron shuttle system involving various cofactors and enzymes, (**c**, **d**) intra-or extracellular localization of AgNPs, (**e**) electrostatic interaction between silver ions and cell wall components, and (**f**) reduction through extracellular enzymes and other organic molecules released into the solution

several side effects and may not be suitable for medical or pharmaceutical purposes (Omidi et al. 2014). The development of biomedical applications has led to the need for a more reliable, nontoxic, and eco-friendly methods of NP synthesis (Braydich-Stolle et al. 2005). Although the log time of used AgNPs has been established, the evidence for silver toxicity is still not clear (Abou El-Nour et al. 2010). Figure 14.2 shows the proposed mechanism of bacteria-mediated synthesis of AgNPs: (a) cellular uptake of silver ions and activation of silver reduction machinery, (b) electron shuttle system involving various cofactors and enzymes, (c, d) intra- or extracellular localization of AgNPs, (e) electrostatic interaction between silver ions and the cell wall components, and (f) reduction through extracellular enzymes and other organic molecules released in the solution (Singh and Shedbalkar 2015). The bacteria may use nitrate anion (NO^{3-}) as a source of nitrogen, leaving behind the metallic Ag ion (Dash 2013). The extracellular synthesis of AgNPs using *Lactobacillus* species is low-cost and effective (Chaudhari et al. 2012). For intracellular synthesis, the bacterial cells are added to the culture medium containing the silver salt and incubated at proper conditions of growth, and the cells are resuspended in sterile distilled water before challenging with silver salt to avoid contamination by the media components

(Singh and Shedbalkar 2015). To obtain AgNPs using intracellular methods, the cells are ultrasonicated (Kalishwaralal et al. 2010). Heat treatment such as autoclaving and the detergents and salts can also be employed to lyse the cells (Fesharaki et al. 2010; Krishnamurthy and Yun 2013). Hence, it is more complicated than the extracellular method.

14.2.2 Characterization

The characterization of NPs is important in understanding and controlling the NP synthesis and applications. Different techniques such as transmission and scanning electron microscopy (TEM, SEM), atomic force microscopy (AFM), dynamic light scattering (DLS), X-ray photoelectron spectroscopy, powder X-ray diffractometry (XRD), Fourier transform infrared spectroscopy, and ultraviolet–visible (UV–Vis) spectroscopy are used to characterize the NPs (Abou El-Nour et al. 2010). The parameters to be determined are the particle size, shape, crystallinity, fractal dimensions, pore size, surface area, orientation, intercalation, and the dispersion of NPs and nanotubes in the nanocomposite materials (Zewde et al. 2016). The morphology and particle size can be measured using TEM, SEM, and AFM. The DLS determines the particle size distribution. XRD is used for the determination of crystallinity, and UV–Vis spectroscopy is used to confirm the sample formation based on the plasmon resonance (Abou El-Nour et al. 2010).

14.2.3 Anti-microbial Activities

The antibiotic-resistant microbes have become a major global concern. It is important to develop newly effective antimicrobial agents that can overcome the multiple antibiotics resistance of the microorganisms (Franci et al. 2015). AgNPs are considered to be novel agents for antimicrobes (Vijayakumar et al. 2013), with good antimicrobial and antioxidant activities (Niraimathi et al. 2013), antifungal, anti-inflammatory, antiviral, anti-angiogenesis, and antiplatelet activities (Caroling et al. 2013). Low concentrations of AgNPs may have no cytotoxicity on human cells, but may be deadly for many viruses and bacteria. The AgNPs may possibly reduce the toxicity on the cells, without affecting the antibacterial efficacy (Karimzadeh and Mansour 2010).

The high antibacterial activity of AgNPs compared with other salts is attributable to their finely sharp surface and extremely large surface area. The antibacterial action of AgNPs (Fig. 14.3) has been proposed as follows:

(a) The small AgNPs penetrate through the cell membrane and create pores to cause cellular leakage.
(b) The intracellular processes are disturbed to provide better contact with microorganisms. The bacterial membrane contains sulfur-containing proteins and the AgNPs interact with these proteins in the cell as well as with the phosphorus-

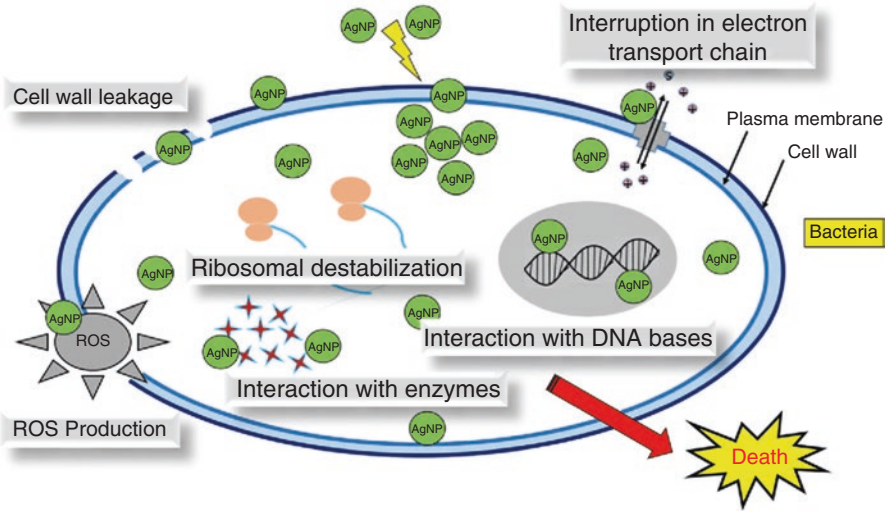

Fig. 14.3 Antimicrobial action of silver nanoparticles (AgNPs) (Adapted from Patil and Kim 2017)

containing compounds such as DNA. Inside the bacterial cell, the AgNPs form a low-molecular-weight region in the center of the bacteria to which the bacteria conglomerates, thus protecting the DNA from the Ag ions.

(c) The AgNPs break the dsDNA.
(d) DNA replication is inhibited.
(e) Interaction with 30S ribosome.
(f) Inactivation of vital enzymes.
(g) Protein is denatured.
(h) Cellular signaling is modulated.
(i) Reactive oxygen species (ROS) is generated, which acts on the DNA and cell membrane.
(j) Ag ions are released, which affect the normal functioning of membrane proteins, and enhance their bactericidal activity. The AgNPs destabilize the plasma membrane potential and deplete the levels of intracellular adenosine triphosphate (ATP) by targeting the bacterial membrane.
(k) Accumulation inside the cells in lethal concentrations results in bacterial cell death (Patil and Kim 2017).

The mechanisms of AgNP-induced cell death are observed in *E. coli* through the leakage of reducing sugars and proteins. The AgNPs destroy the permeability of the bacterial membranes via the generation of many pits and gaps, indicating the damage to the bacterial cell membrane structure (Dibrov et al. 2002; Li et al. 2010; Patil et al. 2012). The AgNPs have greater affinity for the interaction with phosphorous and sulfur-containing biomolecules found in the extracellular (membrane protein), and the intracellular components (DNA bases, protein), which are involved in cell division, respiration, and cell survival (Patil and Kim 2017). The Ag ions display antibacterial activity by interacting with the peptidoglycan cell wall and plasma

membrane (Radzig et al. 2013) and also by inhibiting bacterial DNA replication through the reaction with sulfhydryl groups in the protein (Seth et al. 2011). The Ag ion can damage the protein structures of the bacteria by binding to the thiol and amino groups (Choi et al. 2008). The interaction of the NPs with the thiol group leads to the stimulation of ROS, resulting in the inhibition of respiratory enzymes and then cell death (Holt and Bard 2005; Ninganagouda et al. 2014).

The AgNPs biosynthesized by using *Abutilon indicum* leaf extract exhibit greater antibacterial effects (inhibition zone diameter) on *Staphylococcus aureus* (16.8 mm), *Bacillus subtilis* (18.3 mm), *Salmonella typhi* (14.5 mm), and *Escherichia coli* (17.2 mm) (Ashokkumar et al. 2015). The inoculation of *Ipomea carnea*-AgNPs on a cellulose acetate membrane exhibits a 14 mm inhibition zone against *Mycobacterium smegmatis* (Daniel et al. 2014). The AgNPs synthesized by *Boerhavia diffusa* show greater sensitivity on *Flavobacterium branchiophilum* compared with two other fish bacterial pathogens *Aeromonas hydrophila* and *Pseudomonas fluorescens* (Thakur et al. 2014). Lingo-berry- and cranberry juice-mediated AgNPs show a higher level of activity against *S. aureus*, *B. subtilis*, and *B. cereus*, but a low level of activity against *C. albicans* and food-borne *B. cereus* (Firdhouse and Lalitha 2015). The biosynthesized AgNPs using cell-free supernatants of *Staphylococcus aureus* exhibit significant antimicrobial activity against methicillin-resistant *S. aureus*, followed by methicillin-resistant *Staphylococcus epidermidis* and *Streptococcus pyogenes*, but with only moderate effects against *Salmonella typhi* and *Klebsiella pneumoniae* (Nanda and Saravanan 2009). The AgNP-mediated Broccoli floret aqueous extract are effective against human pathogens such as *Klebsiella pneumonia*, *Staphylococcus saprophyticus*, and *Escherichia coli* (Caroling et al. 2013). The AgNPs become attached to the surface of the cell membrane, disturb the function, and penetrate directly into the bacterial outer membrane and release the Ag ions (Caroling et al. 2013).

14.2.4 Anti-cancer Activities

The discovery and identification of a new antitumor drug with few side effects on the immune system has become major goal in many studies on immuno-pharmacology (Xu et al. 2009). The focus has increased towards developing potent anticancer and antitumor drugs based on the natural compounds from plants and marine bioresources and microorganisms (Devi et al. 2012). Most cytotoxic drugs act on cancer cell growth and division, but the co-application with nanomaterials could revolutionize cancer diagnosis and therapy (Abdullah et al. 2014; Gul-e-Saba and Abdullah 2015; Supraja et al. 2016; Hussein et al. 2020) and the encapsulation of therapeutic agents with NPs could improve targeted drug delivery systems (Abdullah et al. 2014). The use of metallic NPs and medical AgNPs has shown different degrees of in vitro cytotoxicity with the ability for passive or active targeting on any particular diseased cells or tumor tissues (Wicki et al. 2015). To overcome the limitations of conventional chemotherapy, the challenges will be to develop new NPs in single platform-based strategies and to address the physiological barriers, limited carrying

capacity, enhanced permeability and retention effect (EPR), the variability of NPs, and the regulatory and manufacturing issues (Wicki et al. 2015).

Although AgNPs may have low toxicity towards human cells with high thermal stability (El-Kassas and El-Sheekh 2014), the toxicity can be influenced by the availability of chemical, biochemical, and/or biological coatings on the NPs surface (Suresh et al. 2012). The surface charges of the AgNPs could determine the toxicity effects in the cells. The positive surface charge may make the cells more adaptable, allowing them to stay for a long time in the blood stream, as compared to the negatively-charged NPs (Tabata and Ikada 1988). This is pertinent for the regulation of anticancer agent (Tiyaboonchai 2003; Schlinkert et al. 2015). The AgNPs may interact with the thiol-rich enzymes, overlapping with the suitable functioning of the cellular proteins, and inducing changes in the cellular chemistry such as providing relatively high hydrophobicity inside the bovine hemoglobin, which causes a transition from alpha helices to beta sheets, leading to partial unfolding and the aggregation of protein (Shawkey et al. 2013; Supraja and Arumugam 2015). The anticancerous efficacies of the AgNPs synthesized through different sources have been evaluated against the Hep2 cell line (Devi et al. 2012; Rosarin et al. 2013), the HT-29 cell line, the Vero cell line, and breast cancer line MCF-7 (Devi and Bhimba 2012; Hussein et al. 2020). AgNPs synthesized using Acalypha indica Linn. exhibit only 40% cell inhibition toward human breast cancer cells (MDA-MB-231) (Krishnaraj et al. 2014). The viability of MCF-7 cells is also reduced to 50% at 5 μg/mL when treated with AgNPs biosynthesized by *Dendrophthoe falcata* (L.f) Ettingsh (Sathishkumar et al. 2014).

The AgNPs synthesized using *Aloe*, *Magnolia* leaves, and *Eucalyptus* leaves extracted at 2–4 ppm are found to be noncytotoxic to human embryonic kidney 293 cells, as analyzed by the automated InQ Plus equipment (Okafor et al. 2013). The stem latex of *Euphorbia nivulia*-capped AgNPs solubilize in water and act as a biocompatible vehicle for the transport of nanosilver to human lung carcinoma cells (A549) (Valodkar et al. 2011). No cytotoxicity effects of *Aloe vera*-conjugated AgNPs have been observed against human dermal fibroblasts (HDF) cells, but excellent antibacterial activity is reported against *E. coli* even at very low concentration (Zhang et al. 2010a, b). The *Chrysanthemum indicum*-AgNPs also exhibit no toxicity on 3T3 mouse embryo fibroblast cells at 25 μg/mL (Arokiyaraj et al. 2014). The AgNPs synthesized using *Origanum vulgare* exhibit a higher dose-dependent response toward human lung A549 cancer cell line (LD_{50} 100 μg/mL) (Sankar et al. 2013). The AgNPs biosynthesized using *Albizia adianthifolia* leaf extract at 10 and 50 μg/mL, show reduced viability of A549 cells to 21%, and 73%, and the normal peripheral lymphocytes to 117% and 109%, respectively, after 6 h exposure. This suggests that the AgNPs are potentially nontoxic to the normal healthy peripheral lymphocytes (PLs) (Gengan et al. 2013). However, the AgNPs synthesized using the root of *Morinda citrifolia* exhibit 100% cell death against the HeLa cell line at 100 μg of AgNPs (Suman et al. 2013).

The IC_{50} of A549 cells is at 43 μg/mL after AgNP treatment, which induces the cell death by ROS generation, resulting in apoptosis (Govender et al. 2013). The MCF-7 cells treated with *Sesbania grandiflora*-mediated AgNPs at 20 μg/mL, lead to nuclear condensation, cell shrinkage, and fragmentation after 48 h, with Hoechst staining. These changes confirm the activation of DNA repair due to the cleavage of the substrates (Jeyaraj et al. 2013). The Ag (protein–lipid)

nanoparticles (Ag-PL NPs) synthesized using *Sterculia foetida* (L.) seed extracts show cellular DNA fragmentation in HeLa cancer cell lines (Rajasekharreddy and Rani 2014). *Alternanthera sessilis*-mediated AgNPs at 25 µL/mL show complete apoptosis of about 95% against prostate cancer cells (PC3), whereas the growth of MCF-7 is inhibited almost 99% (Firdhouse and Lalitha 2013). *Datura inoxia*-AgNPs inhibit 50% of human MCF-7 proliferation at IC_{50} 20 µg/mL after 24 h incubation by inhibiting its growth, arresting the cell-cycle phases, and reducing the DNA synthesis, to induce apoptosis (Gajendran et al. 2014). The anticancer effects of starch-coated AgNPs have been studied in the normal human lung fibroblast cells (IMR-90) and human glioblastoma cells (U251). The AgNPs show more sensitivity towards U251 cells than the IMR-90 cells by inducing changes in the cell morphology, reducing the cell viability and metabolic activity, and increasing the oxidative stress, leading to mitochondrial damage, increased ROS production, and DNA damage. The cellular uptake of the AgNPs occurs mainly through endocytosis, where the AgNP-treated cells show several abnormalities including upregulation of metallothionein, downregulation of major actin-binding protein, filamin, and mitotic arrest. The morphological changes of the cancer cells suggest that the AgNPs induce the cell death mechanism (Zhang et al. 2016). Figure 14.4 shows the mechanisms of AgNP-induced cytotoxicity in cancer cell-lines through endoplasmic reticulum stress (ER), lactate dehydrogenase (LDH), and ROS. Single-crystalline AgNPs have dose-dependent cytotoxic activity on the MCF-7 breast cancer cells through the induction of apoptosis, with 50% cell growth inhibition (LD_{50}) of 3.5 ng/mL and LD_{100} of 14 ng/mL (Franco-Molina et al. 2010). The ROS elevation caused by the AgNPs could damage the cell DNA as reported in some in vitro studies (Ahmad et al. 2008; Asharani et al. 2009; Foldbjerg et al. 2009).

The AgNPs have shown significant inhibitory effects on the activity of interleukin-5 (IL-5), interferon-γ (INF-γ), and tumor necrosis factor-α (TNF-α) (Shin et al. 2007). The AgNPs could destroy the tumor cells because of their plasmonic nature, where the light from the target cells can be absorbed and converted into thermal energy, leading to thermal ablation of the target cells (Loo et al. 2005; Nurani et al. 2015). The AgNPs may also stimulate cytotoxicity in phagocytosing cells in mouse peritoneal macrophages and human monocytes (Foldbjerg et al. 2009; Park et al. 2010; Shavandi et al. 2011). The Cytotoxicity activity induced through ROS leading to cell apoptosis, could be achieved at a lower AgNPs concentration and low incubation times (Braydich-Stolle et al. 2005; Carlson et al. 2008; Nishanth et al. 2011). The cytotoxic effects of AgNPs on MDA-MB-231 cells, resulting in the inhibition of the cell growth, the activation of LDH, increased level of ROS generation and the activation of caspase-3, are all essentials in the induction of apoptosis (Gurunathan et al. 2013a, b). The AgNPs biosynthesized from *Datura inoxia* extract exhibit anticancer activity after 24 h treatment, by inducing apoptosis in the MCF-7 cells via the ROS-mediated apoptotic pathway, leading to increased ROS levels, followed by the losses of mitochondrial membrane, leading to increased apoptotic morphological changes in the AgNP-treated cells. The DNA content is significantly reduced after staining with propidium iodide (PI), where the control cells exhibit very few PI-positive cells, while the treated cells show gradual increase in the number of PI-positive cells (Gajendran et al. 2014). The *Albizia adianthifolia*-based

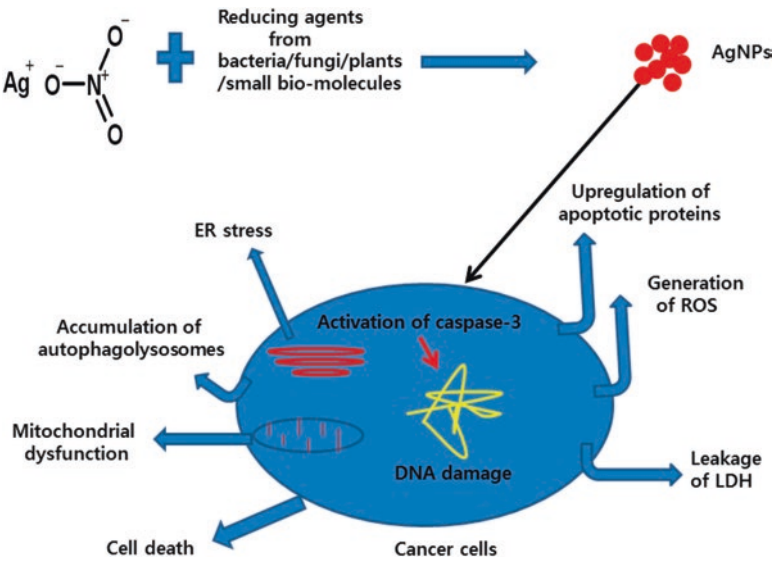

Fig. 14.4 The possible mechanisms of silver nanoparticle (AgNP)-induced cytotoxicity in cancer cell lines. Endoplasmic reticulum stress (ER), lactate dehydrogenase (LDH), reactive oxygen species (ROS) (Adapted from Zhang et al. 2016)

AgNPs have pro-apoptotic activities which activate the intrinsic apoptotic pathway in the lung carcinoma cells (A549) mediated by the CD95 death receptor. This induces the Fas-associated protein with death domain (FADD) adapter protein which binds to and activates caspase-8 through the formation of a death-inducing signaling complex, resulting in reduced CD95 expression and ATP concentrations. The increased level of lipid peroxidation as a result of ROS is also attributable to the disorders in the mitochondrial respiratory chain (Govender et al. 2013).

14.3 Conclusion

Nanoparticles and nanomaterials can be utilized for human medical applications including for the delivery of therapeutic drugs to cells, or for the imaging of tissues and organs. AgNPs have gained special interest for biomedical applications because of their SPR energy, which is located away from the inter-band transition energy, and their antioxidant, antimicrobial, and cytotoxic activities. The development of a reliable and environmentally friendly process for the synthesis of AgNPs is of great importance, especially with regard to meeting the economic and green production route. The mechanisms of AgNP-induced bacteria death include the destruction of membrane structure and permeability via the generation of many pits and gaps, resulting in the leakage of reducing sugars and proteins. The AgNP-induced cytotoxicity in cancer cell lines is through ER stress, LDH leakage, elevated ROS and finally the induction of apoptosis.

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