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REVIEW ARTICLE

Silver nanoparticles as antimicrobial therapeutics: current perspectives and future challenges

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Abstract
Utility of silver metal in antimicrobial therapy is an accepted practice since ages that faded with time because of the identification of a few silver resistant strains in the contemporary era. A successive development of antibiotics soon followed. However, due to an indiscriminate and unregulated use coupled with poor legal control measures and a dearth of expertise in handling the critical episodes, the antibiotics era has already seen a steep decline in the past decades due to the evolution of multi-drug resistant 'superbugs' which pose a sizeable challenge to manage with. Due to limited options in the pipeline and no clear strategy in the forefront, the aspirations for novel, MDR focused drug discovery to target the 'superbugs' arose which once again led to the rise of AgNPs in antimicrobial research. In this review, we have focused on the green routes for the synthesis of AgNPs, the mode of microbial inhibition by AgNPs, synergistic effect of AgNPs with antibiotics and future challenges for the development of nano-silver-based therapeutics.

Keywords AgNPs · Synergistic effect · Multi drug resistance · Antibiotics · Green synthesis

Abbreviations

RT	Room temperature
AgNPs	Silver nanoparticles

Introduction

The later half of twentieth century has witnessed an evolutionary phenomenon of antibiotic resistance. This unique occurance was acknowledgement in the late 1960 with the identification of penicillin resistant *Streptococcus pneumoniae* (Goldstein 1999). By the end of the twentieth century, this phenomenon has witnessed a tremendous outburst and at present, around 80% of the bacterial strains have developed resistance against one or more antibiotics (WHO 2014). Coupled with an indiscriminate, unrestricted and uncapped consumption of antibiotics, the development in these highly evolved superbugs has rendered a whole generation of antibiotics less effective (Fair and Tor 2014; Friedman et al. 2016). Apart from affecting the human health, the research and development for upgrading the existing antibiotics for countering the perils concerning multi drug resistance in bacteria consumes a large chunk of economy (Founou et al. 2017). It is, therefore, highly desirable to improve the present methodologies with innovative strategies having a broad-spectrum mechanism for targeting the superbugs (Karam et al. 2016). The broad spectrum targeting approach achieved by synergistic effect of one or more antibiotics administered as a single formulation has proved to be quite beneficial, but the optimum results are still not achieved (Bush 2017). The aspirations for the development of new generation of antibiotics are, therefore, high for which the metallic nanoparticles present a laudable profile (Hoseinzadeh et al. 2017). As per recent reports, a debatable genotoxicity, cytotoxicity and a low selectivity categorizes AgNPs among the dubious antimicrobial contenders (Fu et al. 2012) but a fine-tuned physicochemical characteristics in terms of size, shape, charge, concentration, and stabilization fortifies their candidature as the prospective new-generation antibiotics (Dakal et al. 2016). Additionally, the release of metal cations generated from the metal nanoparticles, which act as the crusaders in deciding the biocidal potency could be regulated methodically either by

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surface ligand coating, scavenging of peroxide intermediates or by pre-oxidation and particle size reduction (Nagy et al. 2011) thereby favouring an enhanced selectivity and target specificity (Gupta et al. 2016). AgNPs with a large surface area are able to interact and bind to the target cells quite efficiently (Martínez-Castañón et al. 2008; Samberg et al. 2011). This is reinforced by their extraordinary susceptibility to bind to the biomolecules of interest which include the microbial peptides, phospholipids, glycoproteins, membrane polysaccharides, cytoskeletal proteins, lipid vesicles, deoxyribonucleic acid (DNA), messenger ribonucleic acid (m-RNA), and lysozyme (Radic 2015; Wang et al. 2017a, b, c; Wigginton et al. 2010; Huang and Lau 2016). The nanoparticle–biomolecule interaction could also be maneuvered using biomacromolecules as AgNPs stabilizers (Zhang and Yang 2013) which provides additional functionalities to enhance their biocompatibility, bioavailability, bioactivity and also helps in their electrosteric stabilization in the solution (Sanyasi et al. 2016). Specifically, the bovine serum albumin (BSA) stabilized AgNPs have received a commendable response due to their significant applications in drug delivery and stability over a range of intracellular pH (Gnanadhas et al. 2013). Inside the cytosol, the initiation of oxidative stress in the microbial cell by generation of reactive oxygen species (ROS) obtained by decoupling oxidative phosphorylation from electron transport chain due to the deactivation of various enzymes of the respiratory chain is also one of the paramount features of AgNPs (Gurunathan et al. 2013). Another significant advantage of using AgNPs in antimicrobial therapeutics is their ability to modulate the microbial influx/efflux pumps, which are the principal mediators of multi drug resistance, eventually impairing the cellular transport mechanism (Prasher et al. 2018a, b). Furthermore, AgNPs reportedly display a remarkable synergism with some of the most popular antibiotics (Deng et al. 2016; Kavya et al. 2018). The much-anticipated broad-spectrum inhibition profile against the evolved microbes can therefore, be comprehended through a meticulously designed and robustly engineered silver-based nanometallo-antibiotics stabilized with appropriate biomaterials.

Chemical synthesis of AgNPs

The synthesis of nanoparticles comprises conventional methodologies ranging from micro-emulsions (Malik et al. 2012), sol gel synthesis (Sui and Charpentier 2012), hydrolysis and thermolysis (Mahshid et al. 2007; Sharifi et al. 2016). Additionally, the contemporary approaches for synthesis: sonochemical reactions (Sáez and Mason 2009), hydrothermal reactions (Li et al. 2015), flow injection syntheses (Wu et al. 2015) and electrospray synthesis (Mody et al. 2010) are also widely practised. The chemical reduction methods for the production of AgNPs include the conversion of Ag^+ ions into stable and colloidal monodispersed nanoparticles using an organic or inorganic reducing agent in an appropriate organic solvent and in the presence of a suitable stabilizing agent. Typically, citrate (Pillai and Kamat 2004) or ascorbate ion (Qin et al. 2010) or a strong reducing agent: borohydride (Creighton et al. 1979; Suh et al. 1983; van Hyning and Zukoski 1998) converts the Ag^+ ions to the metal atoms. The Ag^0 atoms thus formed further coalesce to oligomeric clusters eventually transforming into AgNPs (Wiley et al. 2005; Evanoff and Chumanov 2004; Merga et al. 2007). A stabilizing agent with –SH (Battocchio et al. 2012; Toh et al. 2014), –OH (Liu et al. 2018) or –COOH (Sambalova et al. 2018) functional group shows substantial interactions with the surface of nanoparticles. It also expedites the particle growth during its binding to the surface of nanoparticles and prevent its agglomeration and sedimentation (Oliveira et al. 2005) in the solution. The stabilizing agent maintains a dispersed state of AgNPs without compromising their surface properties. Some of the recent reports recognized an exceptionally high yield of AgNPs synthesized in the organic solvents that act as reducing agents as well. The nanoparticles obtained by this method are customarily monodispersed with a narrow size distribution (Sun and Xia 2002). Another technique to obtain size-optimized, monodispersed and spherical AgNPs is by polyol process (Feldmann and Jungk 2001; Fievet and Brayner 2013) where the stabilizer is dissolved in a polyol medium followed by the addition of silver salt. Modified precursor injection technique is a hybrid method of the polyol process where an addition of aqueous solution of silver nitrate into hot ethylene glycol using a microsyringe leads to a rapid nucleation. The injection rate and reaction temperature are the critical parameters for this technique to achieve a reduced particle size and monodispersity. Typically, an injection rate of 2.5 ml s^{-1} at a reaction temperature of 100 °C (Kim et al. 2006) yields AgNPs of size 17 ± 2 nm. Dondi et al. (2012) designed a facile, one-step synthetic route for the synthesis of size- and shape optimized AgNPs from tollens reagent using a central resorcinol ether core surrounded by triazole sugar ligands, which promote nucleation, growth, and passivation phases of the preparation of AgNP. This method gives AgNPs of size ranging from 25 to 50 nm (Dondi et al. 2012). The attainment of size and shape optimized AgNPs is also achieved by taking hydrogel template where the nucleation takes place in the existing free space between the networks of hydrogel which also provide a long shelf life to the nanoparticles. This method gives silver nanorods and nanocubes within a size range 1–10 nm (Mohan et al. 2010). The surfactants having oxyethylene groups that oxidize to hydroperoxide thus reducing Ag^+ to silver metal yield colloidal stabilized AgNPs. Liz-Marzan and Lado-Tourino (1996) reported nonionic surfactants such as Brij 92 [poly-(2)-oxyethylene oleyl ether], Brij 72 [poly-(2)-oxyethylene stearyl ether], Brij 97 [poly-(10)-oxyethylene oleyl ether] and Tween 80 [polyoxyethylene-(20)-sorbitan monooleate], which play a critical role in the stabilization and reduction of and ethanolic solution of AgNPs (Liz-Marzan and Lado-Tourino 1996). Dong et al. reported AgNPs of triangular nanoprism shape obtained by a stepwise reduction of silver nitrate with an appropriate molar ratio of sodium borohydride and trisodium citrate, which is critical for the procurement of desired nanoparticles (Dong et al. 2010). A rapid synthesis of size-controlled and self-assembling AgNPs has been reported (Kundu et al. 2009) in the presence of alkaline 2,7-dihydroxy naphthaline as a reducing agent and TX-100 media as solvent. The molar ratio between Ag^+ ion and TX-100 is critical for the transformation of spherical nanoparticles to triangular silver nanoprisms with sizes ranging from 4 to 32 nm. Contemporarily, several polymers have been employed as stabilizing agents for the synthesis of AgNPs, which include: Polyvinylalcohol (PVA) (Kyrychenko et al. 2017), Poly(1-vinyl-1,2,4-triazole) (PVT) (Prozorova et al. 2014), Cyclodextrin (Maciollek and Ritter 2014) Poly-*N*-vinyl-2-pyrrolidone (PVP) (Bajpai et al. 2007), Polyethyleneglycol (PEG) (Simakova et al. 2014), Polymethylmethacrylate (PMMA) (Borse et al. 2016; Kassaee et al. 2011). Chemical methods are, therefore, the most versatile tools for procuring a wide diversity of AgNPs. However, due to the associated toxicities (Marin et al. 2015), use of biologically hazardous chemicals and solvents, impure product formation, sensitivity to environmental conditions (Wang et al. 2017a, b, c; Sharma 2013; Quadros and Marr 2012) and limited yields, the green approaches are required for AgNP synthesis.

Plant mediated green synthesis of AgNPs

The identification of reducing agents that are widely distributed in the biological systems led to the evolution of green synthesis of AgNPs. The plant extract obtained from leaves, barks, roots, flower and seeds contains the essential biomolecules: enzymes, amino acids, proteins, polysaccharides, and vitamins that could efficiently reduce Ag^+ ions to the AgNPs (Velayutham et al. 2013; Merambio-Jones and; Hoek 2010; Bar et al. 2009; Shaik et al. 2018). They may also act as capping agents for the colloidal stabilization of AgNPs (Kumar and Yadav 2009; Chung et al. 2016; Banerjee et al. 2014). Reportedly, the plant metabolites: terpenoids (Mashwani et al. 2016), alkaloids (Almadiy et al. 2017), and polyphenols (Jacob et al. 2008) mediate the bio reduction of metal ions to nanoparticles (Mittal et al. 2013; Makarov et al. 2014). An added advantage of the plant-mediated synthesis of AgNPs is that the plant extract customarily plays a dual role of reducing agent as well as that of a stabilizer (Roopan et al. 2013), Fig. 1. Additionally, the most favored solvent is water in most cases. However, reports have also

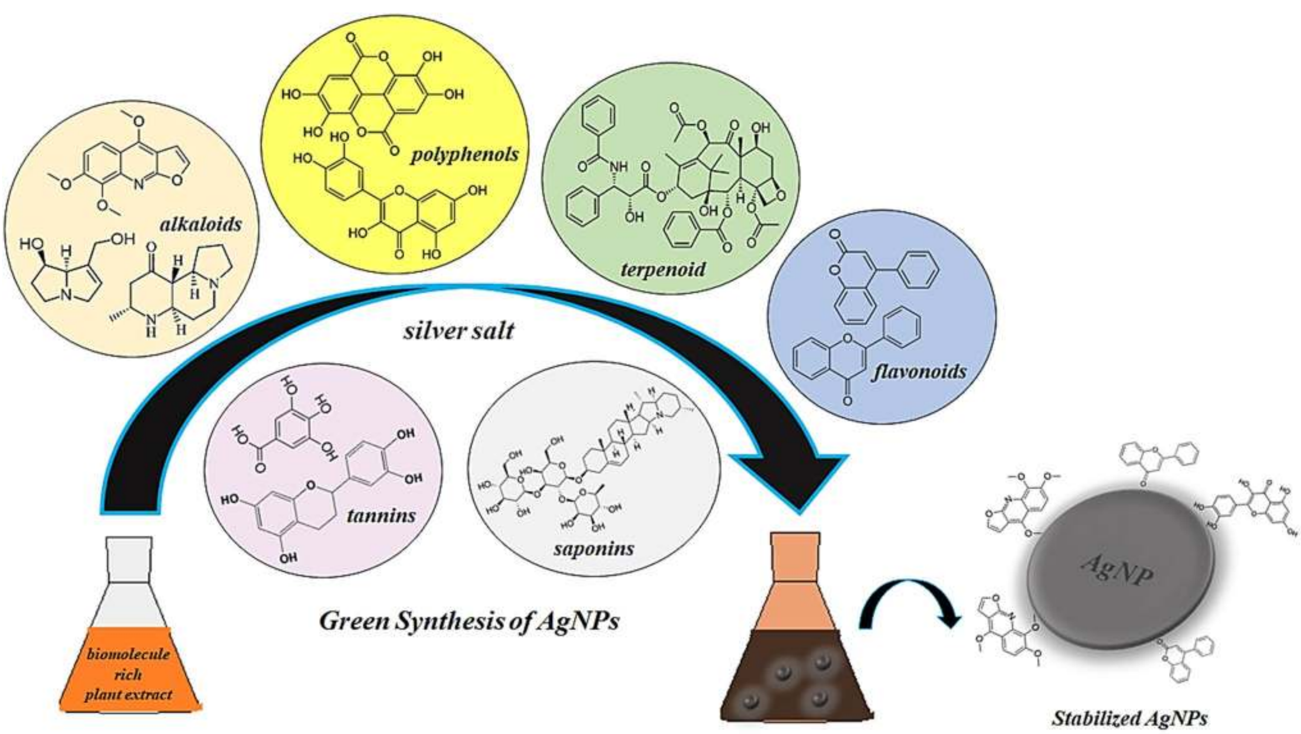

Fig. 1 Plant mediated synthesis of AgNPs

validated the use of organic solvents like methanol, ethanol and ethyl acetate for the same purpose (Sadeghi et al. 2015; Rahimi-Nasrabadi et al. 2014; Shafaghat 2014; Kulkarni et al. 2012; Logeswari et al. 2015). Table 1 presents a brief description of the plant extract mediated synthesis of AgNPs and their morphology. In these examples, the plant extract plays a dual role of a reductant as well as the colloid stabilizer of AgNPs.

Microbe assisted green synthesis of AgNPs

A numerous standardized physical and chemical methodologies effectively used for the synthesis of AgNPs (Zhang et al. 2016a, b) are questionable because of the associated inconsistencies and environmental/health hazards. Moreover, the stabilization of the colloidal suspensions of nanoparticles was also a matter of concern. Hence, the green routes that involve the use of biological reducing agents in the form of macromolecules: peptides, polysaccharides, enzymes, which are environmentally benign, are being among the most acceptable approaches for AgNPs synthesis (Ghodake et al. 2013; Tanvir et al. 2012). These green approaches for AgNPs synthesis comprise the extracts obtained from algae, plants and microbes like bacteria and fungi (Kulkarni and Muddapur 2013). It is also realized that compared to the use of plant extracts and bio macromolecules as reducing and capping agents, the synthesis of AgNPs by microbes requires a great effort and care primarily due to the difficulty in microbial growth, maintaining the microbial culture, standardization of the inoculums sizes, and optimization of the broth environment. A standard method for the synthesis of AgNPs from microbes involves the cultivation of isolated or genetically engineered microbes in a culture media: Luria–Bertani Broth (LB) and malt extract, glucose, yeast extract and peptone (MGYP). The biomolecules present in the culture: peptone, yeast extract, dextrose and other essential growth factors also possess a resilient reducing and stabilizing competence. The synthesis of the AgNPs could be done using microbial biomass collected after discarding the spent media from the cell culture or alternately, by utilizing the spent media (with or deprived of the microbes) treated with silver salts (Liu et al. 2014). Even though an exhaustive mechanism for the synthesis of biogenic AgNPs is unclear, but going by a few reports, the enzymes secreted by the microbe strain under investigation determine the nanoparticle formation. The microbial synthesis of AgNPs could be achieved either extracellularly by directly using the microbial cell biomass or the growth medium containing extracellular materials or it may also be realized intracellularly. (Ajitha et al. 2014; Bhainsa and Dsouza 2006) Reportedly, the intracellular route ensures a superior control over the morphology of AgNPs due to an enhanced compliance to the nano systems (Table 2).

Synergistic effect of AgNPs

Discovery of penicillin in 1928 to treat the microbial infections marked an end to the usage of silver for the same purpose. However, with the development of multi-drug resistance in pathogenic microbes, the research on the antimicrobial efficacy of silver regained momentum. AgNPs have been reported to have myriad applications as biocidal agents (Ge et al. 2014; Wei et al. 2015; Hazarika et al. 2016; Firdhouse and Lalitha 2015; Kuunal et al. 2016; Pulit et al. 2013; Siddiqi et al. 2018; Lara et al. 2011). Reportedly, the therapeutic formulations of AgNPs with the rather ineffective antibiotics of the era displayed a significant synergistic effect with a broad-spectrum mechanism of action (Fayaz et al. 2010; Li et al. 2005; Hwang et al. 2012). The formulation of antibiotics with AgNPs not only improves the permeability of the antibiotic to the target cells, but also enhances the bioavailability. The activity of the antibiotics coupled with AgNPs in *E. coli* and *B. Subtilis* increases eightfold compared to the activity of same antibiotic when used individually (Javier et al. 2016). Additionally, the minimum administrable dose of the antibiotic also lowered due to the presence of AgNPs in the formulation (Ping et al. 2005). Deng et al. (2016), proposed a four-step pathway to elucidate the mechanism for AgNP-antibiotic synergism by working on β-lactam class of antibiotics: Enoxacin, kanamycin, neomycin, and tetracycline. Reportedly, the AgNPs form a complex with the antibiotics thereby enhancing its interactions with the target cells. This event increases the concentration of Ag^+ ions near the target cell eventually leading to its death. Thirumurugan and coworkers deciphered that the pharmacodynamics interaction between the AgNPs and antibiotics leads to an augmented level of reactive oxygen species (ROS), damage of the microbial membrane followed by leakage of K^+ ion and inhibition in the biofilm formation eventually killing the target microbe (Thirumurugan et al. 2016). Locatelli and coworkers reported synergistic effect between AgNPs and alisertib against glioblastoma multiforme where the nanoparticles augmented the effect of the drug leading to a substantial reduction in the in vivo tumor progression (Locatelli et al. 2014). Kovacs and coworkers reported the potential of AgNPs in combinatorial chemotherapy against the MDR cancer. The antiproliferative effect of AgNPs and an inhibitory effect on the efflux activity of the MDR cancer cell lines coupled with a synergistic effect with six different antineoplastic agents on drug resistant cells validated this potency of AgNPs (Kovacs et al. 2016). Daima and coworkers demonstrated a novel approach for improving antibacterial potency AgNPs by their surface

Table 1 Recent reports on synthesis, morphology and applications of AgNPs prepared form plant extracts acting as reducing as well as stabilizing agents

Reducing agent	Conditions	Morphology	References	Application
Filtered aqueous extract of *Caulerpa racemosa* marine algae acting as both reducing and stabilizing agent	1 mM ($AgNO_3$), 3 h, RT Extract: 10 ml/90 ml of $AgNO_3$	Size: 5–25 nm Shape: spherical and triangular	Kathiraven et al. (2014)	Antibacterial action against *Proteus mirabilis and Staphylococcus aureus*
Aqueous filtrate of *Nephrolepis exaltata L. fern* acting as both reducing and stabilizing agent	1 mM ($AgNO_3$), 4 h, RT Extract: 10 ml/90 ml of $AgNO_3$	Size: 24.76 nm (avg.) Shape: spherical	Bhor et al. (2014)	Antibacterial action against *Klebsiella pneumonia* NCIM 2719, *Proteus morganii* NCIM 2719, *Corynebacterium diphtheriae, Pseudomonas testesteroni* NCIM 5098, *Bacillus subtilis* NCIM 2063 and *Escherichia coli*
Aqueous filtrate of *Carica papaya* peel extract acting as both reducing and stabilizing agent	1 mM ($AgNO_3$), 30 min, RT Extract: 2.5–15 ml/100 ml of $AgNO_3$	Size: 10–30 nm Shape: spherical	Kokila et al. (2016)	Activity against Gram-positive bacteria: *Staphylococcus aureus, Bacillus. subtilis* and Gram-negative bacteria: *Klebsiella Pneumonia and Escherichia coli*
Aqueous extract of *Curcuma longa* Tuber	1 mM ($AgNO_3$), stir at RT	Size: 18 ± 0.5 nm Shape: spherical	Alsammarraie et al. (2018)	Activity against *Escherichia coli* O157:H7 and *Listeria monocytogenes*
Petroleum ether extract of *Lantana camara* leaves	1 mM ($AgNO_3$), 24 h, dark, RT	Size: 410–450 nm Shape: spherical	Shriniwas and Subhaah (2017)	Activity against *Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa*
Aqueous fruit extract of *Tamarind Indica*	5 mM ($AgNO_3$), microwave, 180 s	Size: 10 nm (avg.) Shape: spherical	Jayaprakash et al. (2017)	Gram-positive Bacteria: *Bacillus cereus, Staphylococcus aureus, Micrococcus luteus, Bacillus subtilis, Enterococcus species and* Gram-negative Bacteria: *Pseudomonas aeruginosa, Salmonella typhi, Escherichia coli, Klebsiella pneumonia*
Aqueous leaf extract of *Azadirachta Indica*	1–5 mM ($AgNO_3$), dark, RT	Size: 5–20 nm Shape: spherical	Ahmed et al. (2016)	Activity against *Staph Aureus, Escherichia coli*
Aqueous plant extract of carnivorous plants *Drosera Indica, Drosera Binata, Drosera Spatulata, Drosera Muscipula*	4 mM ($AgNO_3$), 2 h, 70 °C followed by cooling, centrifugation at 15,000 rpm for 15 min	Size: variable Shape: spherical	Banasiuk et al. (2017)	Activity against *Staphylococcus Aureus, Pseudomonas Aeruginosa, Candida Albicans* ATCC 90028, *Pectobacterium atrosepticum* SCRI 1043, *Dickeya dadantii* 3937
Aqueous leaf extract of *Ocimum sanctum*	2 mM ($AgNO_3$), 5–35 °C RT	Size: 12–16 nm Shape: spherical	Jain and Mehata (2017)	Activity against Gram-negative bacteria
Aqueous fruit extract of *Carambola*	4 mM ($AgNO_3$), stir 40 °C	Size: 10–40 nm Shape: spherical	Gavade et al. (2015)	Activity against *Escherichia coli* and *Pseudomonas aeruginosa*
Aqueous leaf extract of *Eriobotrya japonica*	1 mM ($AgNO_3$), stir 80 °C	Size: 20 nm (avg.) Shape: spherical	Rao and Tang (2017)	Activity against *Escherichia coli* and *Staphylococcus aureus*

Table 2 Synthesis, morphology, and applications of AgNPs prepared form microbes

Reducing agent	Derived from	Conditions	Morphology	References	Application
Nitrate reductase enzyme of *Fusarium oxysporum*	*Fusarium oxysporum*	10 g fungal biomass AgNO3 (10 mM) in the filtrate (Sigma, St. Louis, MO) and maintained for 72 h at 28 °C	Size: 57.6 ± 1.7 nm Shape: spherical	Fanti et al. (2018)	Activity against promastigote and amastigote forms of *Leishmania amazonensis*
Fungal Xylanases	*Aspergillus niger* L3 and *Trichoderma longibrachiatum* L2	Crude enzyme (1 ml) + 50 ml of 1 mM AgNO3 (30 ± 2 °C)	Size: 15.21–77.49 nm Shape: spherical	Elegbede et al. (2018)	Effective as antimicrobial, antioxidant, catalytic, anticoagulant and thrombolytic agents
Fungal biomass obtained from dried mycelia	*Cladosporium* species	Fungal extract + 10 ml of $AgNO_3$ (5 mM) solution, stirring at RT for 1 h	Mean size: 24 nm Shape: spherical	Popli et al. (2018)	Antioxidant, anti-diabetic and anti-Alzheimer properties
Fungal biomass	*Penicillium polonicum* ARA 10	10 ml fungal filtrate + 90 ml of 1 mM $AgNO_3$ solution, incubation with shaking (200 rpm) at room, in presence of light	Size: 10–15 nm Shape: spherical and oval	Neethu et al. (2018a, b)	Activity against *Salmonella enterica serovar Typhimurium*
Fungal biomass	*Phanerochaete chrysosporium* (MTCC-787)	20 g of fungal biomass + 200 ml of milli-Q, incubation at 25 °C for 72 h + 1 mM $AgNO_3$, incubation at 25 °C for 120 h, RT in a dark room	Size: 34–90 nm Shape: spherical and oval	Saravanan et al. (2018a, b)	Activity against *Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus and Staphylococcus epidermidis*
Mycelial filtrate of Trichoderma atroviride strain KNUP001	*Trichoderma atroviride* strain KNUP001	100 ml cells free fungal biomass filtrate + $AgNO_3$ (5 mM or 10 mM), 40 °C, darkness	Size: 15–25 nm (avg.) Shape: variable	Kumar et al. (2018)	Antibacterial activity against the Gram-positive and Gram-negative bacteria: *Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus*
Mycelial cell free filtrate	*Aspergillus brasiliensis*	$AgNO_3$ + 100 ml mycelial cell free filtrate 0.1 N HCl & NaOH were used to adjust the solution pH	Size: 6–21 nm Shape: spherical	Omran et al. (2018)	Activity against Gram-positive and Gram-negative bacteria: *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Candida albicans*, respectively
Fungal biomass	*Aspergillus niger* JX556221	Fungal biomass + 0.1 mM $AgNO_3$ solution, stirring at RT for 24 h	Size: 20–25 nm Shape: spherical	Wang et al. (2018)	Elevation of ROS levels in target cells, anticancer potential against colon cancer cell line, HT-29
Fungal biomass	*Trichoderma longibrachiatum*	fungal biomass + 100 ml Milli-Q deionized water, stirring for 48 h at 28 °C at150 rpm + 1 mM $AgNO_3$ solution, stirring at 150 rpm at 23–33 °C in dark	Size: variable Shape: spherical	Elamawi et al. (2018)	Activity against phytopathogenic fungi: *Fusarium verticillioides, Fusarium moniliforme, Penicillium brevicompactum, Helminthosporium oryzae, and Pyricularia grisea*

Table 2 (continued)

Reducing agent	Derived from	Conditions	Morphology	References	Application
Fungal biomass	*Penicillium polonicum*	10 ml Fungal cell filtrate + 90 ml of 1 mM $AgNO_3$ solution incubated and shaken (200 rpm), RT, in the presence of light	Size: 10–15 nm Shape: spherical	Neethu et al. (2018a, b)	Antibacterial efficacy against biofilm forming, multidrug-resistant *Acinetobacter baumanii*
Cell free bacterial supernatant	*Streptomyces xinghaiensis* OF1 strain	Supernatant + $AgNO_3$ solution (final concentration 0.001 mol l^{-1}), incubated at RT for 2–3 days	Size:64 (±49) nm Shape: spherical	Wypij et al. (2018)	Activity against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Bacillus subtilis, Candida albicans* and *Malassezia furfur*
Aq. Enzyme extracts from cell free supernatant of bacterium sp.	*Bacillus* sp. (bacillus amyloliquefaciens and bacillus subtilis)	Cell free supernatant. 10 ml of this supernatant mixed with 90 ml $AgNO_3$, stirring at RT to get AgNPs	Size: < 100 nm Shape: spherical	Ghiuta et al. (2018)	Antimicrobial activity against Gram-negative bacteria: *Escherichia coli, Pseudomonas aeruginosa, Salmonella*, as well as Gram-positive: *Staphylococcus aureus, Streptococcus pyogenes*
B. brevis (NCIM 2533) culture broth	*Bacillus Brevis* (NCIM 2533)	Bacterium culture broth + 1 mM $AgNO_3$, overnight incubation and stirring at RT	Size: 41–68 nm Shape: spherical	Saravanan et al. (2018a, b)	Antibacterial property against multi-drug resistant pathogens such as *Salmonella typhi* and *Staphylococcus aureus*
Cell free supernatant of acidophilic actinobacteria culture broth	*Streptacidiphilus durhamensis* HGG16n	Cell free bacterial supernatant + 3 mM $AgNO_3$, incubated at 26 °C, stirring at RT in dark, 7 days	Size: 8–48 nm Shape: spherical	Buszwski et al. (2018a, b)	Antimicrobial activity against *Pseudomonas aeruginosa, Staphylococcus aureus*, and *Proteus mirabilis*, followed by *Escherichia coli, Klebsiella pneumoniae*, and *Bacillus subtilis*
Nostoc linckia extract	*Nostoc linckia*	5 ml Nostoc linckia + 45 ml $AgNO_3$ (1 mM, aq soln.), stirring at RT, 8 h	Size: 5–60 nm Shape: spherical	Vanlalveni et al. (2018)	Activities against *Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, candida albicans* and *Aspergillus niger*
Bacterial Exopolysaccharide	*Leuconostoc lactis*	9 mM $AgNO_3$ in 10 ml milli Q water, stirring at RT in dark, 24 h	Size: 35 nm (avg) Shape: spherical	Saravanan et al. (2017)	Degradation of harmful textile dyes (azo dyes)
Cell free supernatant of bacterial strain	*Actinobacteria* SH11 strain	Preincubated Cell free bacterial supernatant + 1 mM $AgNO_3$, stirring at RT, 2–3 days	Mean size of 13.2 (±2.9) nm Shape: spherical	Wypij et al. (2017a, b)	Activity against Gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and Gram-negative (*Escherichia coli*)

Table 2 (continued)

Reducing agent	Derived from	Conditions	Morphology	References	Application
Wet fungal mycelia	20 different filamentous fungal strains identified as: IPT825, 827, 829, 849, 853, 859, 868, 856, 1005, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, and 1018	Cell free filtrate + $AgNO_3$ (1 mM), incubation at 30 °C, agitation at 200 rpm for 120 h in the dark	Size: 30–100 nm Shape: spherical	Ottoni et al. (2017)	Antimicrobial activity against *Escherichia coli, Staphylococcus aureus*, and *Pseudomonas aeruginosa*
Fungal cell free filtrate	*Cunninghamella echinulata*	$AgNO_3$ (10 mM) solution + aqueous fungal extract, incubation in the dark for 24 h	Size: 20–50 nm Shape: spherical	Anbazhagan et al. (2017)	Activity against *Bacillus subtilis Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae*
Encapsulated biomass beads	*Phoma exigua* var. exigua	Cell filtrate was treated with $AgNO_3$ (1 mM)	Size: 22 nm Shape: spherical	Shende et al. (2017)	Activity against *Escherichia coli* and *Staphylococcus aureus*
Supernatant of endophytic fungus	*Alternaria* species	Mycelium free filtrate (10 ml) + 90 ml of $AgNO_3$ (1 mM), incubation at 40 °C in a hot water bath for 20 min	Size: 10–30 nm Shape: Spherical	Singh et al. (2017a, b)	Activity against *Bacillus subtilis* (MTCC441), *Staphylococcus aureus* (MTCC740), *Escherichia coli* (MTCC444) *and Serratia marcescens* (MTCC97)
Cell free extract of bacterial isolate	*Bacillus methylotropicus* DC3	$AgNO_3$ added to the cell free Supernatant to get final conc. 1 mM, incubation at (200 rpm) centrifugation (20,000 rpm)	Size: 10–30 nm Shape: Spherical	Wang et al. (2016)	Activity against *Candida albicans, Salmonella enterica, Escherichia coli* and *Vibrio parahaemolyticus*
Cell free extract of bacterial isolate	*Pseudomonas aeruginosa* JP2	Cell free extract of bacterial isolate + $AgNO_3$, stirring at RT for 24 h	Size: 5–60 nm Shape: spherical	Ali et al. (2016)	Cost effective method, improved bioavailability
Cell free supernatant at optimum pH < 4	Acidophilic *actinomycetes SL19 and SL24* of *Pilimelia columellifera* subsp. pallida	Cell free supernatant + 1 mM $AgNO_3$, stirring at RT for 2–3 days	Size: 12.7 and 15.9 nm Shape: spherical	Golinska et al. (2016a, b)	Activity against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumoniae*
Cell free bacterial supernatant	ATCC27853 Strain of *Pseudomonas aeruginosa*	*Pseudomonas aeruginosa* culture supernatant (10, 30, and 50% by volume) + $AgNO_3$ (1, 5, and 10 mM), stirring at 37 °C for 24 h	Size: 25–45 nm Shape: spherical	Quinteros et al. (2016)	Bactericidal effects against both Gram-positive and Gram-negative bacterial strains such as methicillin-resistant *Staphylococcus aureus, Acinetobacter baumannii*, and *Escherichia coli*, negligible cytotoxic effect in human neutrophils

modification with the surface corona of bioactive polyoxometalates (POMs) by utilising zwitterionic tyrosine amino acid as a pH-switchable reducing and capping agent of AgNPs. A synergistic antibacterial action of AgNPs and POMs enhanced the physical damage to the Gram-negative bacterium *Escherichia coli* and Gram-positive bacterium *Staphylococcus albus* (Daima et al. 2013, Table 3). Demonstrates the synergistic effect of AgNPs with antibiotics against the target pathogen.

Biocidal effects of AgNPs

Antimicrobial activity of AgNPs

The oligodynamic effect for the AgNPs is most remarkable among all the other metals (Morones et al. 2005a, b; Fabrega et al. 2009; Prasher et al. 2018a, b; Schacht et al. 2012). The biocidal potency of silver is attributed to certain morphological and physicochemical parameters, which include size, shape, colloidal stabilization, surface corona, composition, aggregation behavior, surface coating, surface/volume ratio which when properly tuned, could contribute towards a broad-spectrum inhibitory profile against several pathogenic microbes (Navya and Daima 2016; Ugru et al. 2018; Daima and Bansal 2015). Ultrafine AgNPs with a spherical shape offer a large surface area of contact with the microbial cell wall and the membrane very effectively (Lu et al. 2013; Singh and Prasher 2018). As determined by confocal imaging of the microbial cells treated with AgNPs, clumping and aggregation behavior of the cells has been identified which is a direct manifestation of the stress response (Pooja et al. 2014) induced in the microbe by nanoparticles. At the molecular level, this clumping behavior is in response to the altered chitin levels in the cell wall (Yadav et al. 2015) to which the microbial cells respond by agglomerating with each other. CFW staining assays validated an augmented production of chitin to overcome the stress stimuli (Singh et al. 2018). After successfully breaching the first line of defense in the form of microbial cell wall, AgNPs now set to target the cell membrane (Dakal et al. 2016). The presence of a positive charge on the silver ion generated from the oxidation of AgNPs by the extracellular oxidants expedites the adhesion of the nanoparticle (Sun et al. 2016; Lesniak et al. 2013) on the negatively charged microbial cell membrane because of the electrostatic forces of interactions (Abbaszadegan et al. 2015; Ansari et al. 2013). AgNPs also interfere with the functioning of the enzyme Lanosterol 14-α demethylase which catalyses the bioconversion of lanosterol to ergosterol and hence maintains the structural integrity of the membrane (Jung et al. 2018; Prasher et al. 2018a, b; Chauhan et al. 2015). The GCMS analysis for the microbial cells treated with AgNPs indicate an uncharacteristic augmentation in the production of lanosterol and an abrupt decline in the ergosterol levels indicating the malfunctioning of the enzyme involved in this bioconversion (Prasher et al. 2018a, b). These events induce aberrations in the structural morphology and integrity of the membrane, which eventually progresses to the shrinkage of cytoplasm and its detachment from the cell membrane subsequently leading to cellular necrosis (Yadav et al. 2015; Pooja et al. 2014). The presence of electron dense pits at the sites of damage caused by the AgNPs in bacteria *E. coli* as revealed by transmission electron microscopy (TEM) support that AgNPs mediated disruptive changes in the microbial membrane (Patra and Baek 2017). The AgNPs possess sturdy interactions towards the sulphur containing proteins in the microbial membrane (Siriwardana et al. 2015; Gomez-Tamayo et al. 2016; Duran et al. 2015; Miclaus et al. 2016; Banerjee and Das 2013). These interactions are adequate to irrefutably effect the selective permeability of the microbial lipid bilayer. This happening weakens the membrane based transport activity by impairing the uptake and release of PO_4^{-2} ions and K^+ ions in the microbial cell (Dakal et al. 2016). An unregulated transport across the membrane leads to the loss of vital nutrients, cellular contents and ATP from the microbial cell eventually leading to the cellular necrosis and cell death (Jung et al. 2008; Prabhu and Poulose 2012). Contrarily, some Gram-positive bacteria such as *S. Aureus* possess low susceptibility to the AgNPs (Koprivnjak et al. 2002; Malanovik and Lohnar 2016; van der Wal et al. 1997) compared to their Gram-negative counterparts such as *E. coli*. This is due to the thickness of peptidoglycan layer which is 30 nm in the former compared to a scanty 3–5 nm in the latter (Abbaszadegan et al. 2015; Guzman et al. 2012; Pazos-Ortiz et al. 2017; Acharya et al. 2018). Additionally, the presence of a negative charge on the peptidoglycan layer inactivates the bioactive Ag^+ ions generated from AgNPs thereby raising the resistance of Gram-positive bacteria against the AgNPs (Yuan et al. 2017; Berger-Bachi 2002; Cavassin et al. 2015). The Gram-negative bacteria, which have lipopolysaccharide-loaded membranes providing defense against the chemical attacks (Paterson 2006; Radzig et al. 2013) display similar effects. After completely crushing the first two lines of microbial defense: cell wall and cell membrane, the AgNPs now tend to enter the microbial cells. Further interaction of AgNPs occurs with organelles like ribosomes and mitochondria (Bressan et al. 2013), biomolecules such as proteins and DNA instigating an irrevocable damage to the microbial cellular machinery (Bao et al. 2015; Morones et al. 2005a, b). In some bacteria, the AgNPs induce errors in sugar metabolism through the glycolytic cycle (Al-Shmgani et al. 2016). Reports describing the AgNPs

Table 3 Synergistic effect of AgNPs with antibiotics and the target microbes

Target pathogen	AgNPs + Antibiotic (synergistic effect)	AgNP morphology	Key references
Staphylococcus aureus	Amoxycillin	Size: variable Shape: spherical	Silvero et al. (2018)
Candida albicans	Fluconazole	Size: 30 ± 1 nm Shape: Spherical	El-Adly and Shabana (2018)
Klebsiella pneumonia, Staphylococcus epidermidis and *Staphylococcus aureus*	Gentamycin	Size: 8–45 nm Shape: spherical	Kumar et al. (2018)
Bacillus cereus, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa	Ceftriaxone	Size: 20 nm Shape: spherical	Shanmuganathan et al. (2018)
Candida albicans	Ketoconazole	Size: 10–15 nm Shape: spherical	Prasher et al. (2018a, b)
Pseudomonas aeruginosa, Staphylococcus aureus, and *Proteus mirabilis*, followed by *Escherichia coli, Klebsiella pneumoniae*, and *Bacillus subtilis*	Streptomycin, gentamycin, kanamycin, ampicillin, tetracycline and neomycin	Size: 8–48 nm Shape: spherical	Buszewski et al. (2018a, b)
Acinetobacter baumannii	Doxycycline, tetracycline and erythromycin	Size: variable Shape: variable	Singh et al. (2018)
Enterococcus faecalis	Gentamycin and Chloramphenicol	Size: 20 nm (avg.) Shape: variable	Katva et al. (2017)
Mycobacterium tuberculosis	Rifampicin	Size: 12 nm (avg.) Shape: spherical and cluster	Jafari et al. (2017)
Pseudomonas aeruginosa Biofilms	Tobramycin	Size: 10–20 nm Shape: variable	Habash et al. (2017)
Escherichia coli and *Staphylococcus aureus*	Vancomycin, Streptomycin, Tetracycline, gentamycin, Amoxycillin, Erythromycin, ciprofloxacin	Size: 15 nm Shape: variable	Saratale et al. (2017)
Serratia marcescens	Ampicillin and penicillin	Size: 2–5 nm Shape: spherical	Kumari et al. (2017)
Candida albicans Candida glabrata, Candida geochares, Candida saitoana, Bacillus cereus, Escherichia coli, Staphylococcus aureus, Listeria monocytogenes, Salmonella typhimurium	Amphotericin B, Kanamycin, Rifampicin	Not available	Patra and Baek (2017)
Staphylococcus aureus and *Escherichia coli*	Ampicillin	Size: 20–170 nm Shape: variable	Tippayawat et al. (2017)
Bacillus cereus, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium and *Vibrio vulnificus*	Amoxycillin, Ampicillin, Erythromycin, Kanamycin, Tetracycline	Size: 5–15 nm Shape: spherical	Prema et al. (2017)
Gram-positive and Gram-negative bacteria	Cephalexin	Size: 21 ± 5 nm (avg.) Shape: spherical	Wang et al. (2017a, b, c)
Escherichia coli and *Staphylococcus aureus*	Penicillin, kanamycin, chloramphenicol, ampicillin	Size: 20–167 nm Shape: variable	Kaweeteerawat et al. (2017)
Pseudomonas aeruginosa, Escherichia coli, Bacillus subtilis, Staphylococcus aureus	Curcumin	Size: 25–35 nm Shape: variable	Jaiswal and Mishra (2017)

Table 3 (continued)

Target pathogen	AgNPs + Antibiotic (synergistic effect)	AgNP morphology	Key references
Microcystis aeruginosa and *Phormidium* sp.	*Gentamycin, ampicillin*	Size: 71–201 nm Shape: variable	Satapathy et al. (2017)
Staphylococcus aureus, Vibrio cholera	*Ampicillin and ciprofloxacin*	Size: 35–60 nm Shape: variable	Naik et al. (2017)
Candida albicans, Malassezia furfur, and *Trichophyton erinacei*	*Fluconazole, ketoconazole*	Size: 12.7 nm (avg.) Shape: spherical	Wypij et al. (2017a, b)
Staphylococcus aureus, Escherichia coli	*Ciprofloxacin*	Not available	Ibrahim et al. (2017)
Staphylococcus aureus and *Bacillus subtilis, Proteus vulgaris*	Vancomycin, Gentamycin, Amikacin, Linezolid	Size: 72–85 nm Shape: variable	Rangarajan et al. (2017)
Bacillus cereus, Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli	Ampicillin, Polymyxin, Gentamicin, Chloramphenicol, Penicillin, Amikacin, Tetracycline, Cephalothin, Amoxyclav, Cefpirome, Clotrimazole	Size: 15–20 nm Shape: variable	Moteria et al. (2017)
Escherichia coli, Staphylococcus aureus, Bacillus subtilis and *Klebsiella pneumoniae*	Ampicillin, chloramphenicol, streptomycin and tetracycline	Size:7.22 ± 3.7 nm (avg.) Shape: variable	Phanjom and Ahmed (2017)
Klebsiella pneumoniae	Gentamycin	Not available	Chibber et al. (2017)
Escherichia coli, Staphylococcus aureus	Ciprofloxacin	Size:17 nm (avg.) Shape: not available	Xiong et al. (2017)
Actinobacillus pleuropneumoniae. Actinobacillus pleuropneumoniae and Pasteurella multocida	Penicillin, Gentamycin, Colistin	Size:8 nm and 28 nm Shape: spherical	Smekalova et al. (2016)
Enterobacteriaceae	Cefotaxime, ceftazidime, meropenem, ciprofloxacin and gentamicin	Size: 28 nm Shape: spherical	Panacek et al. (2016)
Bacillus cereus 4079, *Staphylococcus epidermidis* 3615, *Staphylococcus aureus* 740, *Bacillus subtilis* 441, *Escherichia coli* 443, *Salmonella typhimurium* 98, *Klebsiella pneumoniae* 3384, *Serratia marcescens* 97	Streptomycin, Amikacin, Kanamycin, Vancomycin, Tetracycline, Ampicillin, Cefepime, Amoxicillin, Cefetaxime	Size: 20–30 nm Shape: FCC cubic	Jyoti et al. (2016)
Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Staphylococcus aureus and Bacillus subtilis	Kanamycin, Ampicillin, Tetracycline	Size: 5–50 nm Shape:spherical	Rathod et al. (2016)
Escherichia coli, Klebsiella pneumoniae, Bacillus subtilis, Staphylococcus aureus, Pseudomonas aeruginosa	Kanamycin, Tetracycline, Ampicillin	Size: 12.7–15.9 nm Shape:spherical	Golinska et al. (2016a, b)
Staphylococcus aureus	Neomycin, Gentamycin	Not available	Jamaran and Zarif (2016)
Klebsiella pneumoniae, Pseudomonas brassicacearum, Aeromonas hydrophila, Escherichia coli, Bacillus cereus, Staphylococcus aureus, Candida albicans, Fusarium oxysporum, and Aspergillus flavus	Streptomycin, tetracycline, kanamycin, rifampicin, amphotericin B, fluconazole, and ketoconazole	5–30 nm Spherical	Aziz et al. (2016)

mediated DNA damage because of the intercalation of Ag^+ ions between the purine and pyrimidine base pairs are available. This event leads to collapse of the DNA double helical structure followed by an impaired replication phenomenon (Pramanik et al. 2016). To escape the AgNPs mediated damage, some bacterial strains have developed another defense measure: formation of biofilms. A thick glycocalyx sheath, which adheres a colony of bacterial cells to a solid sedentary surface via the weak van-der Waals forces of attraction, expedited the mellowing of microbial biofilm (de Campos et al. 2016; Jung et al. 2008). This glycocalyx matrix also support antibiotic resistance in some bacteria strains by accruing a typical antibiotic molecule up to a quarter of its weight thus regulating its passage in the cell (Singh et al. 2017a, b; Stewart and Costerton 2001). Another important yet critical phenomenon that regulated the selective entry of foreign agents to the bacterial cells is the efflux/influx pumps. Starch stabilized AgNPs have been reported to counter the efflux/influx pumps mediated transport mechanism in the candida cells which was verified through R6G efflux/influx assay (Prasher et al. 2018a, b). Ultrafine AgNPs prepared by plant based bio reductants display remarkable biocidal properties against MDR strains of *E. coli* and *S. aureus*. Some reports describing the AgNPs targeting of the bacterial biofilms without altering the mammalian cell viability are also available. CMT (carboxymethyl tamarind polysaccharide) capped AgNPs with an average particle size of 30 nm are known to restrict the progression of biofilm in both Gram-positive and Gram-negative bacteria (Sanyasi et al. 2016; Singh et al. 2015; Loose and Mitchison 2014). The citrate-capped AgNPs having 10 nm average size display synergistic effect with aztreonam against the *P. aeruginosa* biofilms.The effect is due to an improved permeation of the antibiotic into biofilm matrix (Plyuta et al. 2013; Habash et al. 2014). Additionally, AgNPs are also known to generate reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), hydroxyl radical (OH.), hypochlorous acid (HOCl) and superoxide ion (O_2^-) in the microbial cell which are known to initiate the progression of oxidative stress in the microbial cell (Yilmaz and Spooner 2011; Zhao and Drlica 2014; Zhang et al. 2016a, b; Kim and Ryu 2012). The source of ROS is the dysfunctioning of the enzymes involved in mitochondrial oxidative phosphorylation. These ROS result in the reduction of glutathione (GSH) into glutathione disulfide (GSSG) apparently promoting the oxidative stress, apoptosis and a dysregulation of the oxidative signaling pathways (Ribeiro et al. 2015). Unregulated ROS levels triggered by the mitochondrial stress and a subsequent disabling of anti-oxidant cellular enzymes due to a failed cellular machinery manifests into severe genotoxic effects (Butler et al. 2015), abnormalities in the chromosomes, mutations and commotions in the DNA strands. Figure 2 presents the biocidal mechanism of AgNPs.

Anticancer activity of AgNPs

Besides displaying a substantial oligodynamic effect towards a variety of microbes (Prasher et al. 2018a, b), the AgNPs also exhibit significant biological activities against cancer. The resistance of cancer cells against contemporary medications: oxaliplatin, carboplatin and cisplatin coupled with their debatable toxicity profile has led to the search for novel metal-based anticancer drugs that were earlier limited exclusively to the organic compounds (Prasher and Sharma 2018). Investigations on the molecular mechanisms revealed that the AgNPs mediate apoptosis together with the sensitization of the cancer cells. This has been validated by a synergistic effect of AgNPs with 5-fluorouracil on apoptosis for both uracil phosphoribosyltransferase (UPRT)-expressing and non-expressing cell lines (Gopinath et al. 2008). The regulation of cellular uptake of AgNPs by endocytosis reportedly induces various cellular aberrations, which include mitotic arrest, upregulation of metallothionein and downregulation of major actin binding proteins eventually inducing an instant cell death (Asha Rani et al. 2009; Jun et al. 2010). Customarily, a direct exposure of the target cells to AgNPs require a high concentration of nanoparticles for an effective functioning. To overcome this episode, Nano carrier-mediated delivery of AgNPs to transmit silver to the target cancer cells has led to a superior cell mortality rate of cancer cells at a lower effective dose (Sanpui et al. 2011; Boca et al. 2011). Further insights on the AgNP induced apoptosis in cancer cells have revealed that the adsorption of cytosolic proteins on the surface of nanoparticles could significantly affect the functioning of several vital intracellular factors and may help in the regulation of gene expression (Asharani et al. 2012; Foldbjerg et al. 2012) for metallothionein and heat shock proteins. Recent reports have validated 'Autophagy-induced' cell death as another widely accepted mechanism authorizing the anti-cancer activity of AgNPs (Lin et al. 2014). AgNPs mediate the accumulation of autophagolyssomes thereby inducing autophagy in the cancer cells. The nanoparticles could also function as drug delivery systems by the encapsulating the therapeutic agents and mediating a site-directed transfer to the target cells (Wicki et al. 2015). The nanoparticle-mediated therapy, therefore, could be a suitable alternative for the anticancer chemotherapy. Achievement of an improved specificity, decline in the toxicity and an increment in biocompatibility, however, still remain major challenges in using metal nanoparticles in single platform-based anticancer strategies.

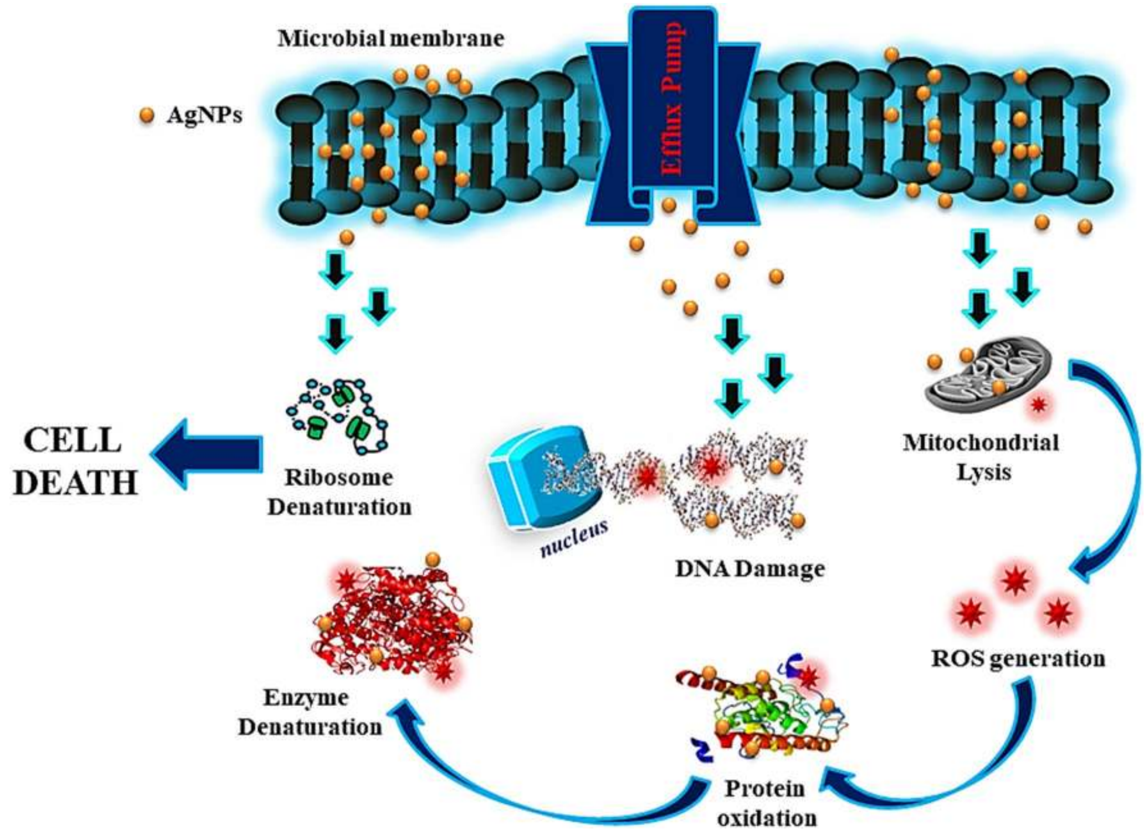

Fig. 2 The various modes of action for the AgNPs mediated biocidal effect

AgNPs in soil management

Pesticidal and Soil Exoenzyme Inhibitory activity: Owing to their single phase synthesis and environment benign, AgNPs had been generated from different sources (plants, microbes etc.) which can be employed for eradicating destructive microorganism from florae and soil to enhance the crop production (Duhan et al. 2017). The pesticidal activity of AgNPs is another extension of their biocidal potency against the invading insects, microbes, worms and larvae, which attack the foodstocks. Moreover, AgNPs possess myriad applications for pesticide mineralization in water that are non-biodegradable and being carcinogenic, deteriorate the quality of ground water. The assimilation of AgNPs on a support usually made of activated carbon and alumina removes the traces of AgNPs in pure water obtained after the mineralization of pesticides. Recently, polymeric membranous supports in the form of cellulose acetate (Manimegalai et al. 2014), polyurethane foam (Manimegalai et al. 2012), reduced graphene oxide (Gupta et al. 2015), methylcellulose polymeric matrix (Velez et al. 2018) have been reported for this purpose. Furthermore, the AgNPs display significant inhibitory activities on the soil exoenzymes related to the soil-nutrient cycle: (urease, acid phosphatase, arylsulfatase, β-glucosidase, dehydrogenase, urease, neutral phosphatase, and alkaline phosphatase) and soil-microbial activity (dehydrogenase, fluorescein diacetate hydrolase) (Shin et al. 2012; Peyrot et al. 2014) which help in effective soil management. The intensity of the inhibitory effect, however, depended upon the concentration of AgNPs (Cao et al. 2017). However, the presence of AgNPs may sometimes negatively affect the soil-friendly bacteria thereby deteriorating its quality (Choi and Hu 2008). The interaction between plant, soil and AgNPs is somewhat complex, but with proper optimization of concentration of silver nanoparticle on foliage and soil can minimize the hazards of nanoparticles over the adsorbent (Pallavi et al. 2016).

Future challenges

The development of nano-silver-based antimicrobial therapeutics is a debatable issue because of the recognition of several silver resistant strains in the past few decades. The discovery of the first silver-resistant bacteria in 1960s from a burn wound treated with $AgNO_3$ (Jelenko 1969) led to their contemporary isolation from several diverse environments (McHugh et al. 1975; Davis et al. 2005; Haefeli et al. 1984; Choudhury and Kumar 1998; Holland et al. 2011). The first attempt to understand the mechanism of microbial resistance against silver was made in 1975 by McHugh and coworkers who identified a plasmid, pMG101, encoding for the resistance mechanism in Salmonella Typhimurium. The efflux pump mediated regulatory mechanism for silver ions was deciphered by Franke (2007), with the identification of SilP, a P-type ATPase efflux pump which transports silver ions from the cell cytoplasm to the periplasm. This discovery facilitated in understanding the transportation mechanism for silver ions from the cell cytoplasm to the periplasm. Parikh et al. (2008) reported the extracellular synthesis of crystalline AgNPs with an average size 20 ± 5 nm using *Morganella* sp., and validated molecular evidence of silver resistance mechanism. Reportedly, the molecular mechanism of silver resistance relates to the expression of three gene homologues: silE, silP and silS as recognized in the microbe. Another breakthrough followed with the identification of a periplasmic protein, Si1F that assists in transportation of Ag^+ from SilP to the SilCBA complex, which forms a cation/proton antiporter system traversing the whole cell membrane. This system belonged to the heavy metal efflux-resistance nodulation cell division (HME-RND) family of efflux pumps. The extension of this by Silver (2003) identified the complex consisting of SilA efflux pump, an outer membrane factor, SilC and a membrane fusion protein SilB that assists in pumping the Ag^+ from the periplasm to the exterior of the cell. Furthermore, the reports have validated the mediation of silver-resistance through the microbial plasmid in *Acinetobacter baumanii*. The bacteria displayed resistance exclusively to silver metal that was due to the activation of an endogenous silver efflux system coupled with porin mutations. Riggle and Kumamoto (2000) identified that the silver resistance phenomenon in candida albicans was due to an ATP-dependent copper efflux protein that was responsible for the removal of Ag^+ from the fungal cells. Though the silver resistance in bacteria could prove to be a breakthrough towards the development of new therapeutics, yet there is a privation of consistent approaches to regulate the bacterial proneness to silver. The dearth of clinically accepted MIC levels further adds to the complications for the interpretation of microbial vulnerability or resistance towards silver (Chopra 2007). Additionally, a recurrent intake of silver causes its deposition in the skin tissues that in the presence of sunlight can cause argyria or argyrosis. Reportedly, the AgNPs also display substantial toxicity against fibroblasts, hepatocytes, osteoblasts or bone-marrow cells (Gaiser et al. 2013). Hence identifying the challenges associated with the silver medications and designing the therapeutics accordingly could aid in the development of a robust class of nano-silver-based new generation antibiotics.

Conclusion

With the identification of MDR superbugs in the twentieth century, the twenty-first century has witnessed an advent of AgNPs as the new-generation therapeutic agents against the pathogenic superbugs. A tunable physicochemical potency of AgNPs presents broad-spectrum activities against the microbes both individually as well as in synergism with the mainstream antibiotics. Additionally, the identification of green synthetic routes catering the need for non-hazardous solvents, reducing and capping agents through these routes also puts the candidature of AgNPs as potential antimicrobials at a stronghold.

Compliance with ethical standards

Conflict of interest Parteek Prasher, Manjeet Singh and Harish Mudila declare that they have no conflict of interest.

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