

Chapter 2

Literature Review

Silver nanoparticles (AgNPs or nanosilver) material has been receiving increasing attention in the recent decade. For example, AgNPs and its application has been studied and exploited to a large extent. In fact, it was reported that nanosilver had a history of approximately 120 years of usage, mainly under the term ‘colloidal silver’ (Nowack et al. 2011). In this proposed study, previous literature was critically reviewed in order to obtain a comprehensive and systematic perspective of this field. These following sections will cover different synthesis of silver nanoparticles and relevant AgNPs-contained materials, antimicrobial effects thereof and mechanisms involved in antimicrobial effects of AgNPs.

2.1 Synthesis of Silver Nanoparticles

Nanoparticles are particles which range from 1 to 100 nm in size. Numerous studies conducted in the past years demonstrated that these materials behave entirely different from their bulky counterparts with regard to the optical, electronic and catalytic properties, etc (Niemeyer 2001; Sun and Xia 2002; Moore 2006). These properties were believed to strongly correlate to the shape, size and substructure of metal nanoparticles. It was stated that properties of nanoparticles could be finely tuned by controlling these parameters (Sun and Xia 2002; Xia et al. 2008). Therefore, it is necessary to summarize synthesis routes and achievements in AgNPs synthesis. In general, there are three key considerations in the synthesis of AgNPs. They are: (1) morphology of AgNPs (mainly size and shape); (2) stability of AgNPs; and (3) feasibility and cost of large-scale production of AgNPs. The following sections would be focusing on these aspects.

2.1.1 Chemically-Synthesized Silver Nanoparticles

Sun and Xia managed to synthesize silver nanocubes of tunable size, 50–120 nm, with PVP as capping agents (Sun and Xia 2002). The size of such AgNPs could be determined by simply adjusting the molar ratio of capping agents. The primary reaction involved a so-called polyol process (reduction of silver nitrate with ethylene glycol at 160 °C) in which ethylene glycol served as both reductant and solvent. This publication served as a basis for controlling shapes, sizes and structures of AgNPs and disclosed the wide possibilities of wet chemistry methods that could be used in this area.

Another shape of silver nanoparticles, nanoprism, was successfully synthesized by Mirkin's group (Jin et al. 2001; Metraux and Mirkin 2005; Millstone et al. 2009). The first reliable synthesis of silver nanoprism was achieved through the photo-induced conversion from silver nanoparticles (Jin et al. 2001). It was reported that prismatic structure of AgNPs could be obtained by irradiation of a conventional 40-W fluorescent light on previously prepared spherical particles (8.0 ± 1.7 nm). As-prepared silver nanoprism had a size with 100 nm in length and 16 nm in thickness. Furthermore, a variety of radiation wavelengths had been found to be capable to induce this conversion, from visible lights to UV irradiation. These achievements were one of the first few synthesis methods that combined light irradiation and chemical reduction, which even paved the way to a broader area of AgNPs synthesis.

Compared with photo-induced synthesis, thermal synthesis (or chemical reduction methods) of silver nanoprism were reported to be able to achieve AgNPs of similar shape and size (Metraux and Mirkin 2005). However, information on purification and stability of such silver nanoprism was not discussed.

Truncated triangular silver nanoplates were slightly different from nanoprism; and synthesis of this specific structure was also appealing to consider due to a proposed mechanism in which different crystal facets may induce different extent of antimicrobial effects (Pal et al. 2007). Typical procedures for synthesis and characterization of truncated triangular silver nanoplates were reported by Chen and Carroll (2002). Three phases were involved in the synthesis route: seeding, growth and aging. First, sodium borohydride (NaBH_4) was used to reduce Ag^+ into $\text{Ag}(0)$ with sodium citrate as stabilizing agent. After this seeding phase, more Ag^+ was reduced by more reducing agents and grew onto these AgNP seeds with cetyltrimethylammonium bromide (CTAB) as capping agent. In the last step, the silver nanoparticles were required to undergo aging in order to allow the particles grow to the expected structure, truncated triangular nanoplates. Centrifugation was required to further remove undesired structures (e.g. rod, sphere, cube, etc.) so as to purify the synthesized nanomaterials.

Among all the nanostructures of silver nanoparticles, studies on spherical particle probably have gained the most attention due to ease of synthesis, purification and application. Great contribution was made by Sondi and his team in developing an easy method to prepare highly concentrated and stable silver nanoparticles

(Sondi et al. 2003). With Daxad 19 as stabilizing agent and ascorbic acid as reducing agent, the as-prepared silver nanoparticles has excellent aqueous stability at a wide range of pH values ranging from 2 to 10. Another advantage of this method is the capability of tuning the particle size between 10 and 30 nm based on the reaction time. This study is vital because high concentration of silver nanoparticles with tunable size is a prerequisite for the comprehensive study of antimicrobial effects of silver nanoparticles (Fig. 2.1).

Most recent advances in AgNP synthesis focus not only on morphology of AgNPs, but on more diverse functionalities as well. Silver was coupled with Fe_3O_4 to accomplish electromagnetic Ag- Fe_3O_4 nanoparticle, which facilitated concentrating and recycling of precious silver (Gong et al. 2007; Li et al. 2014). Silver was also doped into nano-titanium oxide and carbon nanotube to enhance their

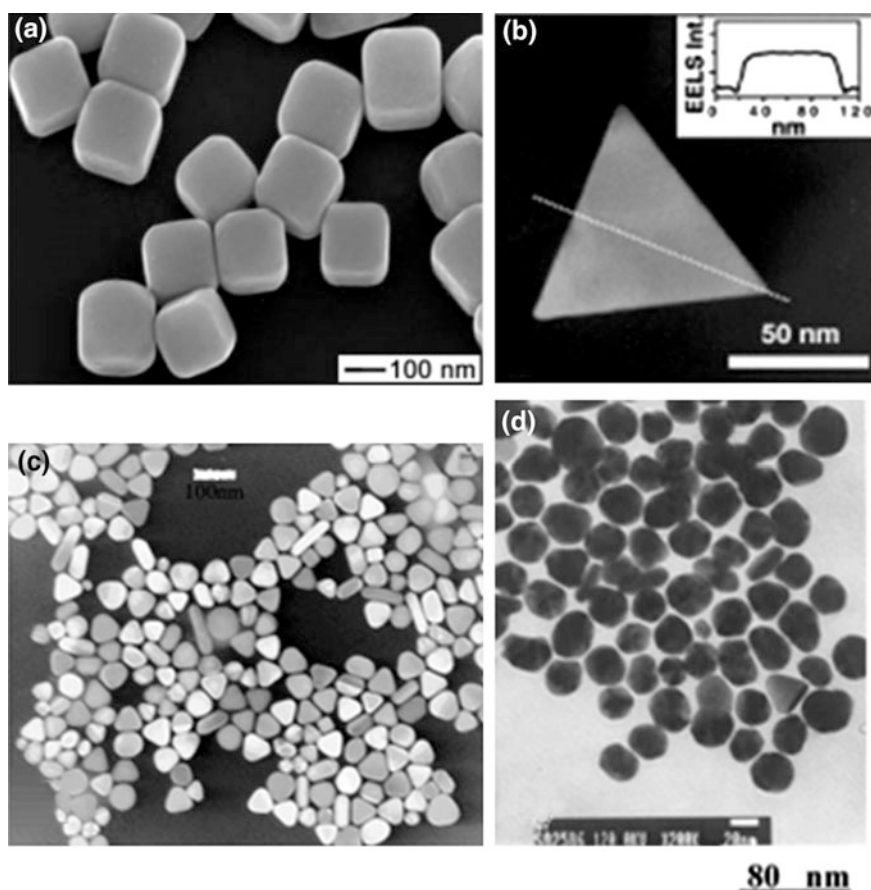


Fig. 2.1 TEM images of different morphologies of silver nanoparticles. **a** nanotubes (Sun and Xia 2002); **b** nanoprisms (Jin et al. 2001); **c** truncated triangle (Chen and Carroll 2002); and **d** stable and adjustable silver nanoparticles (Sondi et al. 2003)

photocatalytic efficiency, showing potential of application in water decontamination (Kim and Song 2014; Ziemkowska et al. 2014). Studies relevant to water disinfection are reviewed in the next section.

Shapes and sizes of silver nanoparticles can be finely tuned; monodispersity can be well achieved. All these advantages rely on the flexibility and diversity of chemicals and synthesis methods. However, the drawbacks of these methods are undeniable: aqueous stability of particles in the long run and involvement of special technology, such as light irradiation. Additionally, intensive chemical usage is a further unfavorable factor, posing some adverse impacts on vulnerable ecological environment.

2.1.2 *Biologically-Synthesized Silver Nanoparticles*

Apart from chemical synthesis, synthesis using biological agents is another vital alternative to produce nanosilver with unique properties. Compared to chemical synthesis, bio-synthesis makes use of biological agents to synthesize and stabilize AgNPs, avoiding usage of toxic chemicals. Synthesis of nanosilver using chemicals benefits from flexibility and diverse method options in laboratory; scaling up such synthesis, however, may be faced with inevitable problems, including high capital cost; high maintenance cost and potential toxicity to eco-system. Biological synthesis methods may make a difference in overcoming these shortcomings typically associated with chemical preparation methods.

Sintubin and co-workers reported that lactic acid bacteria, *Lactobacillus* spp. were capable of reducing Ag^+ into silver nanoparticles (Sintubin et al. 2009). Gram-positive bacteria including *Lactobacillus* spp. and *Enterococcus faecium*, and gram-negative bacteria such as *Pseudomonas aeruginosa* and *Escherichia coli* have been comprehensively screened for nanosilver production. As shown in comparison, *Lactobacillus* spp. was outstanding for its competitive capability in generating silver nanoparticles of smaller size (10–20 nm), more stable dispersion and higher yield. As-prepared nanosilver was situated widely in the cell, in the outer layer of cell and on the cell wall, which is believed to be an advantage in avoiding particle aggregation.

Silver nanoparticles of 10–50 nm could be synthesized by reacting Ag^+ ions with biomass of *Brevibacterium casei* (Kalishwaralal et al. 2010). Such synthesis route required less time (24 h only) and only benign conditions (37 °C). On top of successfully identifying the presence of nanoparticles, Kalishwaralal and his co-workers also found that protein or functional groups may play an important role and initialize this reaction based on Fourier Transform Infrared Spectroscopy (FTIR) results. This study disclosed the secret of bio-AgNPs and may lead to area that could actively select the best microorganism of interest.

Production of highly concentrated nanosilver materials was reported by Juibari et al. (2011). Juibari's team isolated a native extremophilic *Ureibacillus thermosphaericus* strain from hot springs. Interestingly, such bacteria strain was able to

produce AgNPs of adjustable size (10–80 nm) by adjusting the initial concentration of Ag^+ ions as well as the temperature (60–80 °C). This study is important in realizing one idea that non-fastidious and native bacteria could be used directly to synthesize AgNPs at high concentration ($C_{\text{Ag, total}} = 0.1 \text{ M}$). And impressively, the size of AgNPs (13–75 nm) could be easily tuned by adjusting the concentration of AgNO_3 and reaction temperature. However, authors did not monitor the long-term stability of such AgNPs in water.

Ahmad and co-workers successfully achieved extracellular biosynthesis of silver nanoparticles using the fungus *Fusarium oxysporum* (Ahmad et al. 2003). With direct addition of AgNO_3 into a solution of *F. oxysporum* biomass, silver nanoparticles could be obtained after approximately 72 h. TEM images showed that the silver nanoparticles were in a size range of 5–50 nm with severe aggregation. In spite of problem of aggregation, Ahmad's study was one of the milestones that expanded to fungi with regard to bio-synthesis of AgNPs. After that, similar results had been reported using two other types of fungi, *Aspergillus fumigatus* (Bfilainsa and D'Souza 2006) and *Fusarium semitectum* (Basavaraja et al. 2008) (Fig. 2.2).

Not only limited to bacteria and fungi, biosynthesis of silver nanoparticles has been expanded to utilizing biomass from yeast (Kowshik et al. 2003), algae

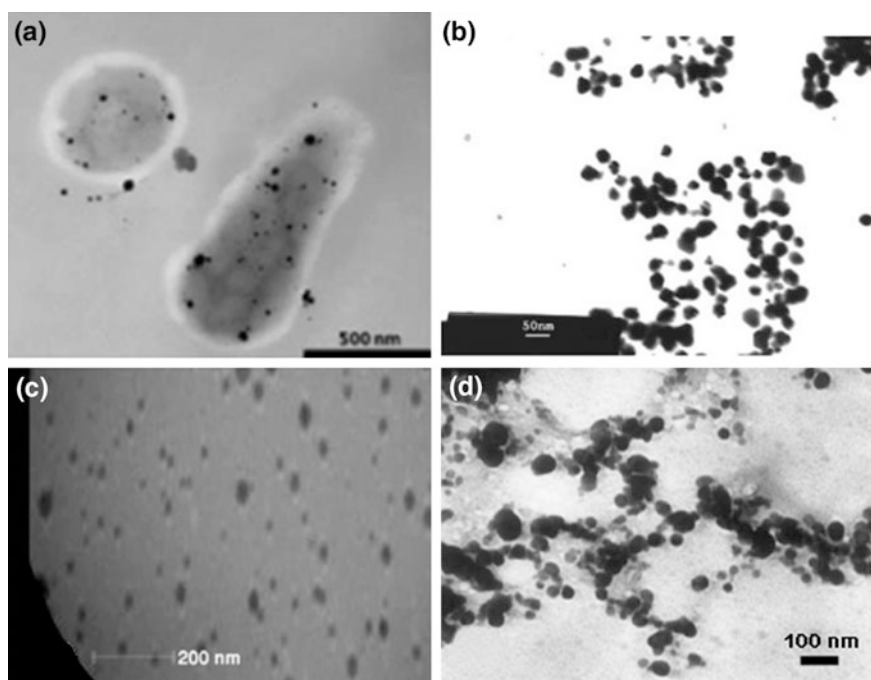


Fig. 2.2 TEM images of AgNPs synthesized from **a** *Lactobacillus* spp. (Sintubin et al. 2009); **b** *Brevibacterium casei* (Kalishwaralal et al. 2010); **c** *Ureibacillus thermosphaericus* strain (Juibari et al. 2011); and **d** *Fusarium oxysporum* (Ahmad et al. 2003)

(Govindaraju et al. 2008) and plants (Rajasekharreddy et al. 2010; Lukman et al. 2011; Veerasamy et al. 2011) as well. Biogenic silver nanoparticles, compared to chemically synthesized, is still new but is developing rapidly in the last five years. Despite the failure of controlling shape, size and purity of AgNPs, biological synthesis is an interesting alternative for chemical methods due to the ease of operation and green synthesis. Additionally the presence of biomass or biological agent may be better to stabilize AgNPs (Sintubin et al. 2009) with better bio-compatibility and less toxicity than heavily used industrial chemicals. It is believed that by choosing the proper biological system, biogenic AgNPs are able to achieve quality close to its peer and find the balance between green synthesis and functionalization (Sintubin et al. 2012).

It is evident from literature that both chem- and bio-synthesis, are intentionally limited to a term 'wet chemistry method'. Being developed for over the past decade, synthesis of AgNPs has also been extended to microwave-aided synthesis, UV-photolysis, electrodeposition, and dry photochemical growth, etc. Nevertheless, it is still worth mentioning that wet chemistry method is by far the most mature and commonly used technique for fabricating AgNPs, considering the capital cost, scalability and feasibility of application (Majdalawieh et al. 2014).

Comparison of chem- and bio-synthesis poses two distinct options: chemical synthesis benefits from finely control of shape/size and monodispersity while biological synthesis benefits from green process and that biomass may serve as a better stabilizing agent. This raises a concern on choosing the right route. Typical chem- and bio-synthesis routes should be selected and compared in view of water disinfection.

2.2 Antimicrobial Effects of Silver Nanoparticles

Silver products have been used for various antimicrobial applications for over thousands of years (Silver et al. 2006); and it won't be surprising to know that nanosilver materials naturally share such excellent property. There are hundreds of publications that involve the antimicrobial effects of AgNPs over the past decade. Specific topics relevant to water disinfection are reviewed below, including effects of silver nanoparticles' properties and water matrices on antimicrobial activities, along with practices of continuous system with AgNPs.

2.2.1 Effects of Silver Nanoparticles' Properties

Morones and co-workers first studied the size effects of nanosilver on antibacterial effects (Morones et al. 2005). Not only characterizing initial AgNPs, those researchers also carefully focused on characterization of the AgNPs after the

experiments, which were found attached on the bacterial cell membrane. Two interesting findings were reported: (1) crystal facet {111} of AgNPs was more likely to attach to the cell membrane, possibly due to the higher atom density and higher reactivity compared to other facets; and (2) most of nanosilver interacting with *E. coli* was in the size range of 1–10 nm. These two findings were consistent: silver {111} facet was higher at the density of atoms while 1–10 nm particles had higher percentage of surface atoms than larger particles. Both findings illustrated that more atoms on the surface was favorable to reactivity of AgNPs, which makes tuning of nanosilver morphology a practical method to enhance the disinfection efficiency.

Inspired by their peers, Pal and coworkers further examined the effects of various shapes of AgNPs on its antimicrobial activities (Pal et al. 2007). By comparing three different kinds of AgNPs, namely spheres, rods and truncated triangle, the researchers concluded that antimicrobial effect of silver nanoparticles was dependent on their shape and nanosilver with truncated triangular shape had the best performance over spherical and rod-shaped counterparts. Proposed reason was in line with Morones et al. (2005): the top basal plane of a truncated triangular nanoplate has a {111} surface, which had higher reactivity to the bacterial surface.

Capping agents, generally, will determine the surface charge of AgNPs that in turn has an impact on antimicrobial ability of AgNPs as described by El Badawy et al. (2011). These researchers studied four kinds of AgNPs with different capping agents, namely H_2 -AgNPs, citrate-AgNPs, PVP-AgNPs and BPEI-AgNPs. These four AgNPs were delicately synthesized so that they had similar size (10–18 nm) yet with distinct surface charge [from the lowest (−40 mV) of citrate-AgNPs to the highest (+40 mV) of BPEI-AgNPs]. Additionally the authors purified these four AgNPs continuously to chip away the impact of released Ag^+ . With such careful experiment design, the effect of surface charge could be realistically studied. They reported that the more positive the surface charge was, the higher toxicity it showed. It was explained by electrostatic barrier between AgNPs and the bacteria used in their study. As we may know, surface of bacteria are negatively-charged because of dissociation of organic groups on the cell membranes, such as Singapore, carboxyl, phosphate and amino groups. Thus, electrostatic barrier was reduced with decrease of negative zeta potential of AgNPs and positively-charged AgNPs even turned such repulsion into attraction, thereby allowing higher chance of interactions. Such physical interactions (i.e. direct contact) were therefore believed to be the primary mechanism for AgNPs toxicity. That is, surface charge was another factor that would affect antimicrobial performances of nanosilver.

2.2.2 Effects of Water Matrices

Diversity of water matrices is always a key consideration when discussing drinking water treatment, especially for water disinfection. Knowing which parameter may

enhance or hinder the antimicrobial effects of nanosilver would equip us with better knowledge to apply nanosilver for water treatment. There are a few publications that have already focused on effects of water matrices on antimicrobial activity of AgNPs. Fabrega et al. (2009) showed that the presence of humic substances was able to completely remove the bactericidal effects of nanosilver. Two milligrams per litre of AgNPs would lead to approximate 80 % inhibition of *Pseudomonas fluorescens*; by contrast, however, no inhibition occurred under same conditions except that 10 mg/L of humic acids was added to the system. Fabrega and coworkers proposed that humic substances might form a film on the NP, thereby reducing the chance of interaction between AgNPs and microbes. This proposed reason was in line with the understanding derived from previous studies (Sondi and Salopek-Sondi 2004; Shrivastava et al. 2007) and those reported in other nanoparticle-related investigation (Baalousha et al. 2008; Diegoli et al. 2008). On the other hand, humic substances could also act as an antioxidant by reacting with any ROS, which is another frequently cited mechanism of AgNPs toxicity (Fabrega et al. 2009). Therefore humic substances could worsen the antibacterial performance regardless of which mechanism is primary.

Jin and coworkers' study was also focusing on such "surface-related mechanism" (Jin et al. 2010). Through study of various combinations of ubiquitous cations and anions on bacterial inactivation of AgNPs, Jin's team found that presence of $\text{Ca}^{2+}/\text{Mg}^{2+}$ ions slightly enhanced the antibacterial performance of nanosilver. Such observation was attributed to these divalent cations being able to form "ion bridge" between negatively-charged AgNPs and lipopolysaccharide (LPS) on cell membrane. The latter is also negatively charged for gram-negative bacteria, *Pseudomonas putida*, used in their study. It was thought that such electrostatic interaction might change the cell membrane permeability and facilitate the transfer of silver nanoparticles into the cells that enabled more AgNPs access to sites of action. This study clearly illustrated that type of electrolytes in water had a direct impact on nanosilver disinfection and study on this area would be a must for further application of AgNPs in water treatment.

On top of Ca^{2+} and Mg^{2+} , other electrolytes also have some impacts on antimicrobial effects of AgNPs. Chloride (Cl^-) is ubiquitous in drinking water and well known for its fast precipitation with Ag^+ . Back to 1998, Gupta and coworkers studied that effects of chloride on toxicity of Ag^+ against *E. coli* (Gupta et al. 1998). It was found that when increasing concentration of Cl^- up to 30 g/L, toxicity of Ag^+ could be enhanced, even when inactivating Ag-resistant species, *E. coli* J53 (pMG101). Such enhancement was believed to be caused by formation of soluble complex ions, AgCl_2^- and AgCl_3^{2-} , at high concentration of Cl^- . This finding was further validated by Choi et al. (2008) and Levard et al. (2013), in which the AgCl colloids (or soluble $\text{AgCl}_x^{(x-1)-}$ species) were found to have as significant toxicity as Ag^+ and AgNPs (Choi et al. 2008; Levard et al. 2013). Most of the concentrations of Cl^- used in the above studies were more than 10 g/L, which was applicable to wastewater treatment and extreme eco-environments, but was rare in drinking water treatment.

Effect of pH is another factor worth considering in the area of water disinfection. Studying the growth of planktonic *P. fluorescens* with AgNPs at different pH (6, 7.5 and 9), Fabrega and her team found that alkaline condition (pH = 9) was preferred in the hope of enhanced toxicity (Fabrega et al. 2009): 90 % decrease of growth in pH 9 while only 10 % decrease in pH 6 at the same dosage of 2 ppm AgNPs. Interestingly, varying pH from 6 to 9 did not change the particle size distribution significantly ($P > 0.05$). Therefore, there is still a gap explaining such pH-related toxicity. Furthermore, El Badawy and coworkers conducted a more comprehensive study on the effect of pH on the particle size of AgNPs (El Badawy et al. 2010). It was reported that whether pH would affect the size was dependent on which capping agent was used. Typically size of sterically stabilized AgNPs (e.g. PVP-coated) tends to remain while sizes of other AgNPs (e.g. citrate-coated) were affected by pH change.

2.2.3 Antibacterial and Antiviral Effects of Silver Nanoparticles

Since Sondi and Salopek-Sondi first studied silver nanoparticles for antibacterial effects on *E. coli* in 2004, there has been a boost of publications that focus on the antimicrobial effects against different microorganisms. Some of the typical and important studies are summarized and discussed below.

Sondi and Salopek-Sondi first studied silver nanoparticles as antimicrobial agent with *E. coli* as a model for Gram-negative bacteria (Sondi and Salopek-Sondi 2004). Silver nanoparticles used in this study was synthesized through reduction of silver nitrate by ascorbic acid (Sondi et al. 2003); and the inhibition experiments were done both in plates and liquid LB medium. Seventy percent of inactivation was reported when 10 mg/L of nanosilver was added whereas nearly 100 % inactivation was observed when 50 mg/L was dosed. Growth inhibition of *E. coli* was successfully observed in experiments of dosing nanosilver into liquid LB medium as well. Nanosilver spread both in and outside of the cell observed by SEM and further TEM images showed that membrane of bacteria was pitted, leaking out the plasma. Equipped with their previous knowledge (Stoimenov et al. 2002), the authors speculated the antimicrobial effects were induced by contact of nanosilver with membrane, increasing permeability and causing cell death thereafter. Although antimicrobial capacity of AgNPs was well reported in this study, its full potential was not well exploited yet.

Other than mechanisms, studies also focused on the synthesis of novel material. Gong and co-workers successfully synthesized magnetic $\text{Fe}_3\text{O}_4@\text{Ag}$ nanoparticles (Gong et al. 2007). Such particles were of sizes ranging from 40 to 80 nm and proven to be able to inhibit the growth of *E. coli* (gram-negative), *Staphylococcus epidermidis* (gram-positive) and *Bacillus subtilis* (spore bacteria). These magnetic

Table 2.1 Summary of literature on the antimicrobial and antiviral effects of AgNPs

Micro-organism	Capping agents	Conc. ^a (mg/L)	Contact time	Major effects	Highlights	References
Bacteria						
<i>E. coli</i>	Citrate/CTAB	0.01–1	0–26 h	Inhibition ^b	Sphere/rod/triangular AgNPs. Triangular was the best	Pal et al. (2007)
<i>E. coli</i>	ND ^c	25–100	ND ^c	Inhibition ^b	AgNPs <10 nm attached to cell membrane. {111} was significant	Morones et al. (2005)
<i>E. coli</i>	Biomass	12.5	2 h	7-log removal	Bio-AgNPs. Antibacterial capacity of AgNPs was similar to Ag ⁺	Sintubin et al. (2011)
<i>E. coli</i>	Triton X-100	10–100	ND ^c	MIC: 70 mg/L	Magnetic Fe ₃ O ₄ @Ag. It could be recycled and reused	Gong et al. (2007)
<i>E. coli</i>	Un-coated	0.2–33 nM	24 h	MIC > 3.3 nM	Bio-AgNPs	Kim et al. (2007)
<i>E. coli</i>	ND ^c	200 as Ag	1 h	6 log removal	Ag@Magnetic hybrid colloids	Park et al. (2013)
<i>E. coli</i>	Saccharide	ND ^c	24 h	MIC > 3.38 mg/L	Ag ⁺ was better than AgNPs in antimicrobial performance	Panacek et al. (2006)
<i>Klebsiella pneumoniae</i>	Saccharide	ND ^c	24 h	MIC > 6.75 mg/L	Ag ⁺ was better than AgNPs in antimicrobial performance	Panacek et al. (2006)
<i>Pseudomonas aeruginosa</i>	ND ^c	25–100	ND ^c	Inhibition ^b	AgNPs <10 nm attached to cell membrane. {111} was reported to be significant	Morones et al. (2005)
<i>Pseudomonas aeruginosa</i>	Biomass	1–500	ND ^c	MBC: 200 mg/L	Bio-AgNPs. Antibacterial capacity of AgNPs was similar to Ag ⁺	Sintubin et al. (2011)
<i>Pseudomonas aeruginosa</i>	Saccharide	ND ^c	24 h	MIC > 3.38 mg/L	Ag ⁺ was better than AgNPs in antimicrobial performance	Panacek et al. (2006)
<i>Pseudomonas putida</i>	ND ^c	0–50	24 h	IC ₅₀ >50	Ag ⁺ was better than AgNPs in antimicrobial performance	Jin et al. (2010)

(continued)

Table 2.1 (continued)

Micro-organism	Capping agents	Conc. ^a (mg/L)	Contact time	Major effects	Highlights	References
<i>S. typhus</i>	ND ^c	25–100	ND ^c	Inhibition ^b	AgNPs <10 nm attached to cell membrane. {111} was reported to be significant	Morones et al. (2005)
<i>Vibrio cholerae</i>	ND ^c	25–100	ND ^c	Inhibition ^b	AgNPs <10 nm attached to cell membrane. {111} was reported to be significant	Morones et al. (2005)
<i>Bacillus spp</i>	Citrate/PVP/BPEI	0.002–1	5 days	Inhibition ^b	BPEI-coated was the best because of positive charge	El Badawy et al. (2011)
<i>Bacillus subtilis</i>	ND ^c	0–50	24 h	IC ₅₀ < 50	Ag ⁺ was better than AgNPs in antimicrobial performance	Jin et al. (2010)
<i>Bacillus subtilis</i>	Triton X-100	10–100	ND ^c	MIC: 70 mg/L	Magnetic Fe ₃ O ₄ @Ag. It could be recycled and reused	Gong et al. (2007)
<i>Enterococcus faecalis</i>	Saccharide	ND ^c	24 h	MIC > 13.5 mg/L	Ag ⁺ was better than AgNPs in antimicrobial performance	Panacek et al. (2006)
<i>Enterococcus faecium</i>	Saccharide	ND ^c	24 h	MIC > 13.5 mg/L	Ag ⁺ was better than AgNPs in antimicrobial performance	Panacek et al. (2006)
<i>Staphylococcus aureus</i>	Biomass	1–500	ND ^c	MBC: 100 mg/L	Bio-AgNPs. Antibacterial capacity of AgNPs was similar to Ag ⁺	Sintubin et al. (2011)
<i>Staphylococcus aureus</i>	Un-coated	0.2–33 nM	24 h	MIC > 33 nM	Bio-AgNPs	Kim et al. (2007)
<i>Staphylococcus aureus</i>	Saccharide	ND ^c	24 h	MIC > 6.75 mg/L	Ag ⁺ was better than AgNPs in antimicrobial performance	Panacek et al. (2006)
<i>Staphylococcus epidermidis</i>	Triton X-100	10–100	ND ^c	MIC: 60 mg/L	Magnetic Fe ₃ O ₄ @Ag. It could be recycled and reused	Gong et al. (2007)
<i>Staphylococcus epidermidis</i>	Saccharide	ND ^c	24 h	MIC > 1.69 mg/L	Ag ⁺ was better than AgNPs in antimicrobial performance	Panacek et al. (2006)

(continued)

Table 2.1 (continued)

Micro-organism	Capping agents	Conc. ^a (mg/L)	Contact time	Major effects	Highlights	References
Viruses						
Adenovirus 3	Tannic acid	50	2 h	>70 % inhibition	AD3 DNA damage observed	Chen et al. (2013)
H1N1 influenza A virus	Glucose and Chitosan	400 as Ag	1 h	Nearly 100 %	AgNPs/Chitosan	Mori et al. (2013)
H3N2 influenza virus	Tannic acid	50	2 h	2.5 log removal	Inactivation in vivo was also reported on mice	Xiang et al. (2013)
Herpes simplex virus type 1	Fungi biomass	10	24 h	80 % inhibition	Mycro-AgNPs	Gaikwad et al. (2013)
Herpes simplex virus type 2	Fungi biomass	10	24 h	50 % inhibition	Mycro-AgNPs	Gaikwad et al. (2013)
Human parainfluenza virus type 3	Fungi biomass	10	72 h	80 % inhibition	Mycro-AgNPs	Gaikwad et al. (2013)
MS2 coliphage	ND ^c	200 as Ag	1 h	2 log removal	Ag@Magnetic hybrid colloids, Recyclable	Park et al. (2013)
U21 bacteriophage	Biomass	5.4	1 min	4.2 log removal	Bio-AgNPs	De Gussemme et al. (2009)

^aThe unit of concentration is mg/L unless specified^bInhibition characterized by unquantified growth delay curve^cND: Not described

$\text{Fe}_3\text{O}_4@\text{AgNPs}$ are attractive because it could be recycled by magnet after interacting with bacteria and reused, providing a new route to compensate for the high price of silver.

Diversity of antimicrobial effects of AgNPs was also extended to viruses. For example, synthesis of AgNPs using fungi biomass was developed and its antiviral effects was evaluated by Gaikwad and co-workers (Gaikwad et al. 2013). Size of silver nanoparticles obtained was 20–40 nm depending on which production systems (i.e. fungi strains) were used. Silver-virus interaction was found to be size-dependent: smaller particles tended to improve the inhibition effects. This finding was in line with previous antibacterial study (Morones et al. 2005), again showing the significance of AgNP size. With contact time (24–72 h), approximate 50–80 % of herpes simplex virus (both type 1 and 2) was inhibited by 10 mg/L of AgNPs. This study did make contributions to the extension of antimicrobial spectrum of nanosilver; however, long reaction time and relatively poor inhibition performance limited application in drinking water treatment process. Increasing the dosage of nanosilver might be a solution in practical use.

There is abundant literature on the antibacterial and antiviral effects of nanosilver in the past decade and relevant studies are summarized in Table 2.1. The majority of literature reviewed here merely focus on inhibition effects with long reaction period and high dosage of AgNPs without considering the capital cost and time requirement needed for water treatment. This gap serves as a purpose of investigating the antibacterial and antiviral effects of AgNPs in terms of both efficiency and cost; that is, shorter contact time, higher antimicrobial performance and relatively lower dosage of AgNPs.

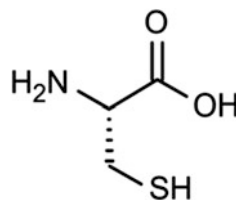
2.3 Antimicrobial Mechanism of Silver Ions and Silver Nanoparticles

Understanding mechanisms of how nanosilver inactivates bacteria and viruses is a crucial route to enhance its disinfection performance. In this section, mechanisms of Ag^+ disinfection are first discussed since nanosilver is always associated with silver ions released from the surface. Literature on intrinsic antimicrobial nature of nanosilver is covered subsequently.

2.3.1 Mechanisms of Aqueous Silver Disinfection

Bactericidal effect of silver ion has been studied for decades (Russell and Hugo 1994); and interaction with thiol groups of the L-cysteine is the most widely known mechanism (Liau et al. 1997). Silver ion has an extremely strong affinity with sulfur ion (S^{2-}) (Eq. 2.1).

Fig. 2.3 Chemical structure of L-cysteine



Consequently there is no doubt that silver would have a strong affinity with thiol groups of protein in cells, thereby inhibiting the activity of essential enzymes and finally inactivating those cells. L-cysteine is a commonly seen amino acid present in protein that contains thiol group (Fig. 2.3).

Kim and co-workers (2004) studied the synergetic effects between Ag^+ and UV-A/visible lights and they noted that this synergy was related to this silver-cysteine interaction. Briefly UV-A (or visible light) could catalyze the formation of silver-cysteine complex and this complex undergoes a photochemical reaction, producing cysteine-dimer (see Eqs. 1.1–1.3 in Chap. 1)

Second mechanism of silver ion disinfection is the interaction between ionic silver and DNA. It was reported that DNA molecules of *E. coli* became condensed after Ag^+ treatment and it was observed through TEM characterization (Feng et al. 2000). Such condensation is believed to occur naturally and it could render the incapability of DNA replication. Whether condensed DNA molecules are attributed to silver-DNA combination or it is only a defense reaction of *E. coli* still remains a question. Nonetheless, one thing is certain: silver ions have interaction with DNA molecules as reported in other literature (Rahn and Landry 1973; Rahn et al. 1973). This Ag-DNA interaction could be utilized to enhance disinfection performance: it was reported that there was a significant synergy between UV and silver ion and this synergy could be applied as a feasible disinfection strategy (Butkus et al. 2004, 2005).

Park and coworkers proposed and proved another mechanism behind aqueous silver disinfection: silver-ion-mediated reactive oxygen species (ROS) generation (Park et al. 2009). These authors used bacterial reporter strains to specifically respond to superoxide radicals ($\text{O}_2^{\cdot-}$). Results showed that more than 50 % of log inactivation resulted from generation of $\text{O}_2^{\cdot-}$ when inactivating either *E. coli* or *Staphylococcus aureus*. This ROS mechanism well explains the fact that silver ions exhibit better disinfection performance in aerobic condition than in anaerobic condition.

2.3.2 Antibacterial Mechanisms of Silver Nanoparticles Disinfection

To date, antimicrobial effects of nanosilver have not yet been understood thoroughly. Many researchers proposed that releasing Ag^+ from the surface of

nanoparticles may be one of mechanisms because antimicrobial effects of Ag^+ were comparable or even better than that of AgNPs (Li et al. 2008; Zodrow et al. 2009; Sintubin et al. 2011). This observation was supported by some of the cases, but there were also other studies in which nanosilver disinfection could not be simply attributed to the silver ion released from the nanoparticles (De Gussemme et al. 2009; Yin et al. 2011).

Thus far there have been limited studies that systematically discuss the intrinsic nature of nanosilver in terms of antimicrobial effects. This question remains challenging mainly due to the fact that suspension of nanosilver in water is always inevitably associated with releasing Ag^+ . This point of view is in agreement with El Badawy et al. (2011). In supporting material of El Badawy et al. (2011), the authors listed 20 publications in which purification of nanosilver suspension (i.e. removing Ag^+ from nanosilver) was not explicitly mentioned. Therefore, it is difficult to investigate the roles of Ag^+ and AgNPs respectively and determine the main cause to which the observed microbial damages were responsible.

Though it was difficult to distinguish the contributions of NP from that of ions, Fabrega and co-workers managed to find some evidence for the existence of AgNPs' 'extra' effects (Fabrega et al. 2009). It was found that introducing the humic substances into the system was able to mitigate the bactericidal effect of AgNPs, yet had no impacts on toxicity of silver ions. In the presence of such humic substances, the toxicity of AgNPs could have persisted if Ag^+ had been the main mechanism. Thus comparing the distinct observations of microorganisms interacting with AgNPs and Ag^+ in the presence of humic substances could serve as a proof that Ag^+ was not the primary mechanism of AgNPs toxicity.

El Badawy and co-workers' study may provide us with some direct hints on the intrinsic antimicrobial effects of AgNPs as well (El Badawy et al. 2011). In their study, four types of silver nanoparticles, uncoated H_2 -AgNPs, citrate coated AgNPs, PVP coated AgNPs and branched polyethyleneimine (BPEI) coated AgNPs, were chosen to study the relative toxicity against *Bacillus* species. One of the highlights of this study was using a continuous flow purification system to wash away any Ag^+ released so as to obtain simply the nanoparticles. The reduction of impurities was indicated by reduction in suspension's conductivity and further confirmed by X-ray photoelectron Spectroscopy (XPS) and proton Nuclear Magnetic Resonance (H-NMR). Reduction in toxicity was observed after the purification, which was most likely caused by the removal of Ag^+ , proving Ag^+ did contribute to the bactericidal effects. This study further found that these four types of AgNPs studied were of the similar sizes (10–18 nm) but significantly different in toxicity against bacteria tested. The only possible reason for this observation was the difference in surface charge. Zeta potentials of these AgNPs were -22, -40, -12 and +39 mV, for H_2 -AgNPs, citrate-AgNPs, PVP-AgNPs and BPEI-AgNPs, respectively. Considering the electrostatic interaction between negatively-charged bacteria membrane and various AgNPs, BPEI-AgNPs (+39 mV) may attract the surface of bacteria, expressing the highest toxicity. As for another three AgNPs, toxicity should be in line with electrostatic repulsive force: the most negatively-charged AgNPs has the highest repulsive electrostatic force, being the least toxic. The observed results well verified

this hypothesis: citrate-AgNPs (-40 mV) showed the lowest toxicity and the positively-charged BPEI-AgNPs the highest. Moreover, this theory was in line with the study on effects of Mg^{2+} and Ca^{2+} (Jin et al. 2010) and the case of bactericidal nano-MgO (Stoimenov et al. 2002).

El Badawy's study is of great importance in understanding the intrinsic bactericidal mechanism of nanosilver. Yet this surface-related physical interaction was not fully capable of addressing some questions. For instance, if the electrostatic force was the main cause, one could expect that gold nanoparticles of positive charges would attract and inactivate any negatively-charged bacteria, such as *E. coli*. Yet majority of studies reported the opposite, that gold nanoparticles did not have any antimicrobial effects against *E. coli* (Hwang et al. 2008).

Hwang et al. (2008) applied stress-specific bioluminescent bacteria to study the toxic mode of AgNPs. These special strains were sensitive to oxidative damage, protein/membrane and DNA damages, respectively. If any above-mentioned damage occurred, corresponding gene could be induced and strongly expressed, responding bioluminescence signal. Through such experiments, the entire procedure of bactericidal effects of AgNPs was described as follows: silver ions produced from AgNPs moved inside the bacterial cell, generating superoxide radicals and other ROS via reaction with oxygen. At the same time, AgNP itself damaged the cell membrane (Morones et al. 2005) and this in turn led to the cell being unable to extrude the Ag^+ , which enhanced the killing effects of Ag^+ . This observation explains why AgNPs caused more damage than Ag^+ did. Hwang concluded that AgNPs (including Ag^+ released) caused toxicity via protein and membrane damage but did not induce DNA damage.

Systematic study of antibacterial activities of AgNPs was not investigated until the advent of Sintubin et al. (2011). In their study, Sintubin and co-workers investigated independently three commonly proposed mechanisms behind antibacterial activities of AgNPs, namely release of Ag^+ , generation of ROS and direct contact (Sintubin et al. 2011). In order to study the contribution of Ag^+ release, minimal inhibition concentration (MIC) and minimal bactericidal concentration (MBC) and log removal of bacteria were determined and compared between AgNPs and Ag^+ . Results showed that the antibacterial profiles of AgNPs and Ag^+ were the same or comparable, indicating the major contribution of bactericidal effects may be attributed to Ag^+ . Impacts of ROS generation by AgNPs were investigated by comparing antibacterial activities under different O_2 percentages. This experimental design was based on one assumption that different O_2 percentage could directly affect the amount of ROS generated. If antibacterial effects mainly relied on ROS generated, different O_2 percentages would reflect on differences in antibacterial activities. Results obtained from their observation indicated that ROS generated by AgNPs most probably contributed only to a minor extent. Lastly, study on direct contact was done by measuring cell membrane permeability and by introducing dialysis membrane. Measurement of cell membrane permeability could quantify the membrane damage induced by AgNPs and introducing dialysis membrane could explicitly help us understand the difference with or without the

presence of direct contact. The results obtained clearly indicated an insignificant role of direct contact in antibacterial activities of AgNPs.

In their study, Sintubin et al. (2011) also provided practical and useful experiment strategies to study the AgNP mechanism. Nevertheless, there was still room for improvement in methodology reported in their study, such as lack of study in DNA damage.

2.3.3 Antiviral Mechanisms of Silver Nanoparticles Disinfection

Compared to bacteria, viruses have huge differences that may have impacts on resistance to AgNPs and inactivation mechanisms thereof. Firstly, size of virus generally is smaller than bacterium. For instance, size of MS2 bacteriophage is approximate 25 nm while size of *E. coli* is approximate 1 micron. The size difference may lead to difference in mode of contact with AgNPs. Secondly, virus lacks cellular structure. Shell of virus only consists of protein coat and in some cases, lipid envelope surrounding the coat. In contrast, bacterial membrane has a more complicated structure, which involves lipopolysaccharides (gram-negative bacteria), peptidoglycan, protein, etc. This structure difference could also lead to difference in mode of contact with AgNPs. Thirdly, viruses do not have metabolism. Intact protein capsid and undamaged genome translates into the infectivity of virus. On the other hand, bacteria reproduction cycle requires more enzyme functions. Any intervention of these functions may lead to loss of bacterial infectivity.

Considering the huge difference between bacteria and viruses, antiviral mechanisms could be significantly different from antibacterial mechanisms. In spite of the well-documented antibacterial mechanism, systematic understanding of antiviral mechanisms of AgNPs remains a gap although some observations have been more or less reported by previous literature.

Elechiguerra et al. (2005) may be one of the earliest studies that observed interaction of AgNPs with viruses, HIV-1 specifically. Through analysis of TEM images and high angle annular dark field (HAADF) images, Elechiguerra and co-workers claimed that interaction with the gp 120 knobs of HIV was one of the major mechanisms of AgNPs to inhibit viral attachment to host cell, leading to overall inhibition of HIV infection (Elechiguerra et al. 2005). This conclusion was further confirmed by other study (Rogers et al. 2008). Similarly, TEM images of H3N2 influenza virus and adenovirus interacting with AgNPs showed that noticeable damage of the capsid was clearly proven and morphology (structure) of virus particle was breached and broken (Chen et al. 2013; Xiang et al. 2013). Furthermore, DNA copies of adenovirus decreased significantly after the AgNPs treatment in a dose-dependent manner, suggesting AgNPs are able to cause damage to gene as well. This point of view was shared by other studies (Lu et al. 2008; Lara et al. 2010). It is worth of reviewing the study of Lara et al. (2010) because the

authors provided an innovative aspect of studying modes of antiviral actions by looking into the roles of AgNPs in different stages of HIV-1 life cycle. It was reported that AgNPs exerted anti-HIV effects at an early stage by inhibition of viral entry or attachment to cells. Besides, AgNPs also inhibited post-entry stages of virus life cycle, most probably by blocking HIV-1 proteins.

Compared to massive publications on antibacterial mechanisms, there have been limited studies on antiviral mechanism thus far. Furthermore, most of the studies in this part focus merely on viral damage, either capsid damage or genome damage. However, complete mechanism study must consist of studies on both AgNPs (antiviral agent) and viruses (target). Study on AgNPs is to find out what is the key property that determines the antiviral effects. Answering this could help us develop better nanosilver. On the other hand, study on viruses is to investigate what types of viral damage has been caused. Investigation of viral damage caused by AgNPs will equip us with a better understanding of virus behaviours after AgNPs treatment.

2.4 Continuous Disinfection System with Silver Nanoparticles

Many efforts have been put in application of AgNPs in continuous flow-through system. Review of previous literature shows that AgNPs has been successfully incorporated in many materials or devices to serve as disinfectants, such as polymer foam (Jain and Pradeep 2005), ceramic materials (Oyanedel-Craver and Smith 2008; Lv et al. 2009), filter paper (Dankovich and Gray 2011) and membrane (Zodrow et al. 2009; De Gusseme et al. 2011). Detailed review is presented below.

Polyurethane (PU) foams were soaked in Ag@citrate NPs suspension for coating overnight by Jain and Pradeep (2005). After saturated coating, such AgNPs-contained PU foams were washed repeatedly to remove any adsorbed ions and then air-dried. With a flow rate of 0.5 L/min, 120 L of *E. coli*-contaminated tap water (10^5 CFU/mL) were passing through the PU foams and no *E. coli* colonies were found in further enumeration. Effective as this material may be, the authors failed to answer one key question: how much AgNPs were incorporated in PU foam after soaking and washing. Lack of quantification of AgNPs in PU foam may jeopardize the reproducibility of the entire experiment. And due to the same reason, it was impossible to discuss whether or not this material was economically beneficial.

With similar 'soak-and-absorb' method, Lv and coworkers synthesized AgNPs-contained ceramic composite (Lv et al. 2009). The highlight of this study was that modification of amino groups on the ceramic surface by using 3-aminopropyltriethoxysilane was conducted to ensure a better absorbance of AgNPs. Results indicated that such ceramic composite was also able to inactivate all the initial *E. coli* (10^5 CFU/mL for 500 mL) at a flow rate of 10 mL/min. This 'soak-and-absorb' strategy was easy to control but difficult to quantify the AgNPs usage. On top of this 'soak-and-absorb' strategy, Oyanedel-Craver and

Smith (2008) provided another method to fix AgNPs onto ceramic filter: painting. Straightforward as it was, concentrate suspension of AgNPs was painted on the filter surface for economical usage of AgNPs. These two ways of fixing AgNPs on the surface did not make a significant difference in terms of disinfection performances. Over 6 log inactivation of *E. coli* were achieved for at least 90 min. Ionic silver release was monitored and the concentrations of all the samples were lower than 0.1 mg/L, which was in compliance with WHO and USEPA recommendations (WHO 2006).

Dankovich and Gray synthesized nanosilver *in situ* with the presence of filter paper in order to generate a bactericidal filter paper (Dankovich and Gray 2011). Water spiked with bacteria was vertically passing through such filter paper with simply gravity. It was noted that more than 7 log removal of *E. coli* and 3 log of *Enterococci faecalis* were achieved. The researchers also monitored the concentration of releasing Ag^+ to make sure it was not higher than 0.1 mg/L. The combination of AgNPs and a paper sheet shed some light on the development of light, cheap, portable and point-of-use water purification device.

Besides antibacterial performance, antiviral effects of AgNPs-involved continuous system were also studied. Zdrov et al. (2009) synthesized membranes with AgNPs impregnated by means of the 'phase inversion' strategy. The silver-impregnated membrane showed strong inactivation capacity against MS2 coliphage as well as *E. coli* K12, and *Pseudomonas mendocina* KR1. Another team from Belgium has also considered viral inactivation using biogenic nanosilver immobilized in polyvinylidene (PVDF) fluoride membranes (De Gussemme et al. 2011). Continuous flow system was built up with such nanosilver-contained membrane to examine the viral inactivation of UZ1 bacteriophage. With a flow rate of 0.375 L/h and a hydraulic retention time (HRT) of 1 h, the continuous flow system could achieve around 4 log removal of UZ1 after 2 h and the concentration of Ag^+ in finished water was as low as $27 \pm 8 \mu\text{g/L}$.

These studies provide invaluable experience on how to implement AgNPs in a continuous flow system and have undeniable achievements on antimicrobial effects of AgNPs. However, these studies ignore several challenges. Firstly, water matrices of real water are reported to affect the antimicrobial effects of AgNPs but not considered in those studies. Secondly, the long-term performance of such continuous flow system was not investigated. In addition, recovery methods after continuous usage need to be addressed.

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