**Review**

**Biosynthesis of Silver Nanoparticles: Minireview**

Alaa M.E. Alnaimat¹; Intesar M.S. Aljamaeen²

¹The karak health affairs directorate, The Jordanian Ministry of Health, Jordan
²Directorate of Education for the area of Madaba, Ministry of Education, Jordan

*Corresponding Author: niamatala@gmail.com*

**Abstract:** In principle, nanoscience focus on the understanding of the structure, physical and chemical properties of nano size objects. Nanoscience and nanotechnology are both recent and active ongoing branch of science includes multi interdisciplinary sciences. On the other hand, nanotechnology considered as the invested outcomes of the obtained fundamental knowledge about nano objects in various commercial, industrial, environmental and medical sectors. All nano scale matters regardless of their nature referred to as nano-objects were the prefix ‘nano’ mean one millionth of millimeter size. Due to their nano size and high surface area, metal nanoparticles exhibits unique and novel physical and chemical properties compared to their macro scale counterparts. They are considered as very interesting and popular antimicrobial agent with wide spectrum activity against the variety of pathogenic bacteria and fungi. Three main methods were routinely used for metal nanoparticles formation that are chemical, physical and biological approaches. As eco-friendly, cheap and safe synthesis approach without the use of toxic chemicals and free of resulted hazardous byproducts several extracellular and intracellular biological methods using bacteria, fungi, plants or their extracts were reported that known collectively as green nanotechnology.

**INTRODUCTION**

Natural nanomaterials can be produced from plants, water bodies, dusts and erosion. They also produced by human activities from combustion, construction, industrial processes and vehicles. Meanwhile engineered nanomaterials are chemical substances or materials that are engineered with particle sizes between 1 to 100 nanometers (Calderón-Jiménez *et al*., 2017).

Objects recognized as nanoparticles are particles with 1 to 100 nanometer in size (Shah *et al*., 2015; Khan *et al*., 2017). According to the International Organization for Standardization (ISO) nanoparticles are a discrete nano-object where all three Cartesian dimensions are less than 100 nm. Also they similarly defined the two-dimensional nano-objects and one-dimensional nano-objects (Shah *et al*., 2015). This nanometer in size particles have surrounding interfacial area that affecting all of its properties (Nguyen *et al*., 2014) which might be ions, inorganic or organic molecules. Regardless of their size, the bulk of a specific material generally have fixed physical properties meanwhile at the nanoscale the same materials behave differently which mean change in material properties as the size reaching nanoscale (Shah *et al*., 2015; Khan *et al*., 2017). The major physical properties of nanoparticles includes high mobility, the distinguishable high specific surface area and their quantum effects (Navya and Daima, 2016).

However, nanoparticles were extensively used in basic and applied research as very useful and astonishing materials due to their high specific surface area and nanoscale size besides many other physical and chemical properties. However, their nanoscale size might potentially have harmful and toxicological effects if released in uncontrolled manner into the environment. They can be seriously harmful if leaked to the soil, water and human health as they absorbed to the food chain or inhaled by organisms. Therefore, risk assessment of their potential harmful effects were highly recommended (Wilson, 2018; Reidy *et al*., 2013; Tolaymat *et al*., 2010).

**Biological and biomedical applications of silver nanoparticles**

Silver is one of the rare naturally occurring elements in our planet. Silver exist in nature in metallic form, insoluble in water, and as silver salts that are soluble in water such as silver nitrate and silver chloride. Both forms, metallic silver and silver salts, have been used in treatment of different mental and physical medical conditions, infectious
diseases, burns and as fungicide (Lara et al., 2011). Recently, silver salts were used in the production of silver nanomaterials in the form of nanoparticles and films. Silver nanoparticles (SNPs/AgNPs) are 1-100 nm three dimensional objects that based on their size and shape have unique and different optical, electrical and magnetic properties compared to larger size counterparts. Silver nanoparticles are interesting nanoscale objects that incorporated in the variety of biomedical applications such as antifungal, antiviral, anti-inflammatory, anti-angiogenic, anticancer and antibacterial agents (Zhang et al., 2016).

Silver nano-particles show potent antifungal activity against various human and plant fungal diseases as well as indoor fungal species. They are proved effective antifungal agent against Trichophyton mentagrophytes and Candida species. The preparation of inert matrix containing AgNPs in soda lime glasses or monodisperse Nano-Ag sepiolite fibers shows enhanced fungicidal activity. As synergetic action with fluconazole the biologically-synthesized AgNPs showed enhanced antifungal activity against Phoma, Fusarium, Trichoderma, and Candida species (Vahabi K et al., 2011). Compared to the conventional antifungal agents the AgNPs stabilized by sodium dodecyl sulfate showed enhanced antifungal activity against Candida albicans (White et al., 2002). It is previously revealed that the enzyme production increased with the decrease in carbon concentration in the growth media (Allimoun et al., 2015; Khleifat and Abboud, 2003; Aljundi et al., 2010; Aljundi and Khleifat, 2010). Thus reflecting the amount of silver AgNP-biosynthesizing enzyme(s). The antifungal activity of the silver nanoparticles were also reported against several phytopathogenic fungi such as Alternaria alternata, Sclerotinia sclerotiorum, Macrophomina phaseolina, Rhizoctonia solani, Botrytis cinerea, Curvularia lunata, Fusarium oxysporum (Salem et al., 2011).

Interestingly, the antiviral activity of silver nanoparticles against several types of viruses such as HIV virus, hepatitis B virus, influenza virus, herpes simplex virus (HSV) and human parainfluenza virus type 3 were reported (Sun et al., 2005; Shammukh et al., 2006; Panyala et al., 2008; Lu et al., 2008; Galdiero et al., 2008; Mehrbod et al., 2009; Lara et al., 2010). In addition, the anti-inflammatory actions of silver nanoparticles to overcome inflammatory action of inflammatory agents have been previously reported (Nahrendorf et al., 2008). Silver nanoparticles were also reported as anti-angiogenic molecules to overcome angiogenic-related diseases (Jo et al., 2015). In association, silver nanoparticles were extensively explored as alternative anticancer agents that can target tumor cells specifically. In their work, (Gopinath et al. 2008) observed that AgNPs not only induce apoptosis but also sensitize cancer cells. It was reported that the cellular uptake of AgNPs occurred mainly through endocytosis and starch-coated AgNPs reported to induce changes in human glioblastoma (U251) cells ending with DNA damage (Hahm, 2004). Other work suggests that the biologically synthesized AgNPs could induce cell death very significantly (Morones et al., 2005). Furthermore, the prepared silver-embedded magnetic nanoparticles were used specifically for targeting breast-cancer cells and floating leukemia cells (Jun et al., 2010). It was reported that the anticancer property of fungal extract-produced AgNPs against human breast cancer is stronger than the bacterial extract-produced AgNPs due to the type of reducing agents used for the synthesis of AgNPs (Gurunathan et al., 2013).

Many research efforts recently explored silver nanoparticles as alternative antibacterial agents to antibiotics to overcome the bacterial resistance against antibiotics issue. It was found that the predominant bactericidal mechanism of AgNPs is the contact killing and surface-immobilized nanoparticles are better than colloidal AgNPs. AgNPs accumulated in the cell wall of Escherichia coli forming pits which eventually leads to cell death (Gurunathan et al., 2009). This mechanism of action on Escherichia coli cells was also approved through the leakage of reducing sugars and proteins as AgNPs able to destroy the permeability of the bacterial membranes via the generation of many pits and gaps (Sondi and Salopek-Sondi, 2004). However, (Morones et al. 2005) proposed that the mechanism of antibacterial activity of AgNPs against Gram-negative bacteria divided into three steps. First, small nanoparticles (1–10 nm) attach to the surface of the cell membrane disruption its permeability and respiration. Second, they penetrate inside the cells and interact with sulfur-and phosphorus-containing compounds such as DNA causing more destructive damage. Third, through releasing silver ions from AgNPs further damage can occur ultimately leads to cell death. It was also reported that the antibacterial activity of AgNPs is size, dose and shape-dependent (Morones et al., 2005; Montes-Burgos et al., 2010).

AgNPs showed high antimicrobial and bactericidal activity against yeast, Gram-positive and Gram-negative bacteria, including highly multi-resistant strains such as methicillin-resistant Staphylococcus aureus and methicillin-resistant Staphylococcus epidermidis (Feng et al., 2000; Sondi and Salopek-Sondi, 2004; Morones et al., 2005; Song HY et al., 2006). Furthermore, the antibacterial and antibiofilm efficiencies of various antibiotics
against different pathogenic bacterial strains were increased in the presence of AgNPs compared to AgNPs or antibiotics alone. Interestingly, among the nanomaterials tested (Silver and titanium dioxide) against routine disinfectant chlorhexidine in Streptococcus mutans AgNPs had the strongest antibacterial activity (Besinis et al., 2014). In vitro different plant extracts could be synergized with biosynthesized AgNP for the enlargement of the antimicrobial activities (Zeidan et al., 2013; Khleifat et al., 2006; Khleifat, 2006; Al-Tawarah et al., 2020; Khlaifat et al., 2019; ALrawashdeh et al., 2019; Jaafreh et al., 2019).

**Biological synthesis of silver nanoparticles**

Three approaches have been used in silver nanoparticle synthesis namely physical, chemical and biological. In physical methods, evaporation-condensation and laser ablation were used for the synthesis of AgNPs (Magnusson et al., 1999; Mafune et al., 2000; Mafune et al., 2001; Dolgaev et al., 2002; Kabashin and Meunier, 2003; Sylvestre et al., 2004; Jung et al., 2006). Physical methods are known for their short time production, using radiation as reducing agent without hazardous chemicals. But the lack of uniform distribution, low yield and solvent contaminations is their main drawbacks (Mafune et al., 2000; Dolgaev et al., 2002; Kabashin and Meunier, 2003; Sylvestre et al., 2004; Jung et al., 2006). However, in chemical methods three main components were involved includes metal precursor, reducing agent and stabilizing/capping agents dissolved in water or organic solvents (Link et al., 2000; Kim et al., 2005; Kawasaki, 2006; Tarasenko et al., 2006; Khleifat et al., 2006; Khleifat et al., 2007; Khleifat et al., 2019). In contrast to the physical methods, chemical methods results in high yield products. But similar to the physical methods, chemical approaches also suffered from several disadvantages such as the materials used in chemical synthesis are expensive, toxic and hazardous (Tsuji et al., 2002), low purity product (Wiley et al., 2005) that accompanied with too many toxic and hazardous by products.

As alternative, the green synthesis of silver nanoparticles was proposed as efficient and eco-friendly process involving natural reducing, capping, and stabilizing agents (Qaralleh et al., 2019; Ankamwar et al., 2005). The bio-reduction of silver salts to silver nanoparticles by the action of biomolecules such as enzymes/proteins, amino acids, polysaccharides, and vitamins is simple, cost effective, dependable, and environmentally friendly approach. Various microorganisms and biological molecules including bacteria, fungi, plant extracts, and small biomolecules like vitamins and amino acids are used in AgNPs synthesis (Klaus et al., 1999; Ghosh et al., 2003) (Figure 1). Three factors distinguish silver nanoparticles synthesis using biological systems including aqueous solvent, the biological reducing agent and unemployment of toxic materials. The size and shape of the resulted biologically synthesized silver nanoparticles are controlled with minimum particle aggregation, high solubility in water, stability and well dispersed which important requirement in various biomedical applications (Panáček et al., 2006) (see Figures 2-4). Optimization of the synthesis process by varying the amount of silver precursor, temperature, pH, and the amount of reducing agent offer control of shape, size, and distribution of the produced nanoparticles.

![Figure 1. Summary of silver nanoparticle biosynthesis process](image-url)
Several studies reported the synthesis of AgNPs using bacteria, fungi, plant extracts and several biomolecules. The first report documented the use of bacteria in silver nanoparticles synthesis involve the bacterial strain *Pseudomonas stutzeri* AG259 that isolated from silver mine. The most widely accepted mechanism of silver biosynthesis is the presence of the nitrate reductase enzyme (Duran et al., 2005). When compared to bacteria, fungi produces and release larger amount of reducing agents that eventually produces larger amounts of silver nanoparticles. Although the exact mechanism of fungi silver nanoparticles biosynthesis is not fully understood it’s reported that fungi synthesize nanoparticles by trapping of Ag⁺ ions at their surface followed by enzymatic reduction of silver ions using naphthoquinones, anthraquinones and nitrate reductase enzymes (Jha et al., 2009). In contrast to the use of plant extracts, using bacteria and fungi is very slow process that represents their main drawbacks. In addition to the advantages mentioned earlier for the biologically synthesized nanoparticles, using plant extracts in silver nanoparticles synthesis are quicker than bacteria and fungi. The mechanism of silver nanoparticles formation employing plant extracts depend on the various phytochemicals available in the plant extracts such as terpenoids, flavones, ketones, aldehydes, amides, and carboxylic acids. Several studies suggested that the phytochemicals play an important and direct role in the formation of nanoparticles through the direct reduction of silver ions to silver nanoparticles (Sakamoto et al., 2009).

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