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REVIEW ARTICLE

Inhibitory effect of silver nano-particles on multidrug resistant *Staphylococcus aureus*: a review

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Abstract

Nanotechnology is an emerging science involving the utilization of nanoparticles. Silver nanoparticles are relatively safer to use because they exhibit no toxicity to the host cell as well as these particles are also able to treat inflammatory conditions and have better results than steroids. Silver nanoparticles can be used to treat the various diseases originating from *Staphylococcus aureus* (stomatitis, mental illness, epilepsy, nicotine addiction and gastroenteritis*). Staphylococcus aureus* is a gram-positive bacterium that is extremely harmful pathogen both for animals and human being. *S. aureus* is highly lethal that infects multiple systems of the body including blood, lungs and skin. *S. aureus* has a very high tendency to develop antibiotic resistance. This resistance is plasmid mediated. Therefore, to counteract this property, the role of silver nanoparticles (AgNPs) were evaluated. After performing multiple experiments, it was observed that AgNPs were highly effective against multidrug resistant *S. aureus*. These evaluations were conducted by observing inhibition zone using different shape, size and concentrations of AgNPs. Best results were obtained by using spherical shape, 2-5 nm AgNPs. An inhibition zone of 53.9% was achieved as compared to hexagonal and pentagonal having larger size 50-100 nm that exhibited 42.8 % inhibition zone. It means that small sized AgNPs have more potential to produce antibacterial activity against *S. aureus* as compared to available antibiotic groups. AgNPs are getting more attention in scientific community due to their broad-spectrum range in medical applications and for their uses in food products. On the basis of previous findings, it's worth mentioning that AgNPs exhibit strong antibacterial activity and can be utilized as an alternative of antibiotics.

Keywords

Antibiotics
Multidrug resistance
Silver nanoparticles
Staphylococcus aureus

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Introduction

Nanotechnology is a developing field of science which involves the development of nanoparticles for various applications due to their volume to surface properties (Nanda & Saravanan, 2009). Silver nanoparticles (AgNPs) are usually lesser than 100 nm having 20-15000 atoms (Chen & Schluesener, 2008). Nanoparticles are famous for their antimicrobial activity (Choi & Hu, 2008; Taglietti et al., 2014). Historically, silver particles have been used widely for many purposes. Silver particles used as ornaments and jewelry. Silver jewelry, wares and ornaments were considered as beneficial for their health (Salata, 2004; Kim et al., 2007; Shahverdi et al., 2007; Lara et al., 2010). Silver salts are used to treat various diseases such as mental illness, nicotine addiction, epilepsy, stomatitis and gastroenteritis (Alidaee et al., 2005; Amin et al., 2007).

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AgNPs treated cloths are helpful to minimize the hospital infections originating from *Staphylococcus aureus* (Durán et al., 2007).

S. aureus is a gram-positive bacterium and the most frequent pathogen present in joint and bone infections (Sendi et al., 2011; Corrado et al., 2016; Kavanagh et al., 2018). *S. aureus* is present everywhere in soft tissues, blood and urinary tract infections (Arrecubieta et al., 2006; McCaig et al., 2006; Besier et al., 2007; Corey, 2009). Main concern is infection of prosthetic joint leading to failure of joint substitute surgery in which infection of hip joint is most common. However, an elevating level of multiple resistance of drug pathogen has presented and is causing high rates of failure in ongoing treatment (Campoccia et al., 2006). AgNPs have got attention due to their broad spectrum antibacterial and long term activity (Kim et al., 2007). Nowadays, AgNPs are used as additive in biocide in many areas including textiles, machines, washings and toothpaste (Prabhu & Poulose, 2012; Vance et al., 2015). For medical applications, about 75% of AgNPs are used in nano-enabled products (Yohan & Chithrani, 2014).

Nanoparticles of silver release ions which react with water to produce reactive oxygen species (ROS). These species enter in the cell membrane leading to cell damage which ultimately results in cell death (Chudobova et al., 2013). Recently, it has been reported that antibacterial potential of AgNPs is due to the generation of free radicals (Kim et al., 2007). It has been observed that the most frequent *S. aureus* infections in the hospitals are infective endocarditis, urinary tract infections, impetigo, bacteremia, pneumonia and cellulites (Tong et al., 2015). The harmful effects of *S. aureus* are able to contribute two important factors. One is the plasmids and staphylococcal cassette chromosome mec (SCC Mec) (Méric et al., 2015). Plasmids are the extra chromosomal part of DNA that initiate resistance in multiple *S. aureus* clones (Shearer et al., 2011). Second is the virulence factor of *S. aureus* having wide spectrum that initiate pneumonia and endocarditic like problems (Baran-Raunstrup et al., 1998). AgNPs are one-dimensional, small sized (1-100 nm), wide spectrum anti-bacterial, anti-viral and having anti-fungal activities (Chernousova & Epple, 2013). AgNPs bind with plasma membrane causing the destabilization of plasma membrane that ultimately results in leakage of proton (Gogoi et al., 2006). AgNPs treated cloths are helpful to minimize the hospital infections originating from *S. aureus* (Durán et al., 2007). Figure 1 showed cellular lysis S. aureus by generating reactive oxygen species using AgNPs.

Antibacterial effect of AgNPs: The antibacterial effect of silver nanoparticles is size dependent. Size of 1-10 nm have been shown to exert direct interaction with cell surface and bacteria (Morones et al., 2005). Later on further studies have shown the effect of silver nanoparticles against staphylococcus cell wall peptidoglycan especially decomposing the peptide part. Glycan consist of N-Acetyl muramic acid and N-Acetyl glucosamine. Silver nanoparticles attach and destroy these bonds and ultimately leading to the release of muramic acid. As a consequence of which pit formation occurred on cell membrane (Mirzajani et al., 2011).

Previous findings have shown the antibacterial effect of silver nanoparticles having diameter ranges from 2.90-11.25 by stabilizing in chitosan and gelatin polymeric matrix. This study was done to check the effects of silver nanoparticles against *Staphylococcus aureus* by using disc diffusion method. They found that silver nanoparticles were showing inhibition zone of 9.9 nm in *Staphylococcus aureus* (Krishna & Miller, 2012). Further studies have shown the different concentrations of silver nitrate against *staphylococcus aureus* infections after burns. At the lowest 0.5% solution of silver nitrate was effectively used against bacteria in laboratory on broth and agar and on burns in vivo. When dressing was moistened with this solution, the grafts were taken more easily. This AgNO3 solution also has no toxic effect on developing epidermal cells. So they found that AgNo3 was effective against *staphylococcus aureus* infections resulting from burns (Bader, 1966).

Many researchers conducted the experiments that hydro gels having high moisture contents when prepared in combination with $AgNO_3$, exert promising toxic effects on *S. aureus*. $AgNO_3$ is also used in creams to treat the inflammatory conditions such as contact dermatitis, atopic dermatitis and psoriasis. $AgNO_3$ is more efficient in comparison with steroids to treat such conditions. It has no cytotoxicity, resistance and reduce erhythema after 1 day treatment (Bhol et al., 2004). Further studies revealed that cell division is restricted in initial stages in *S. aureus* when its contact with $AgNO_3$ and produced morphological alterations, ultimately resulted in cell lysis (Jung et al., 2008). Alkawareek et al. (2019) have performed experiments to check the antibacterial effects of silver nanoparticles against *S. aureus*. The bacteria was treated with 1 mM AgNP for 1 hour exposure time and resulted in bacteriostatic effect in *S. aureus*. Further experiments were done to evaluate the antimicrobial effect of staphylococcus aureus at different concentrations by using Agar well diffusion method. Figure 2 showed inhibition zone against *S. aureus* at different $AgNO_3$ concentrations.

Nanda & Saravanan (2009) have reported that synthesized silver nanoparticles using *S. aureus* supernatant to decrease silver ions aqueous solution. These biogenic AgNP showed outstanding antibacterial effects against *S. aureus*. It has been concluded that silver nanoparticles are more efficient than antimicrobial agents. The antimicrobial potentials of AgNP were checked by disk diffusion method at different concentrations. Increasing the concentrations of AgNPs resulted in increasing the inhibitory effects on *S. aureus* as shown in Figure 3.

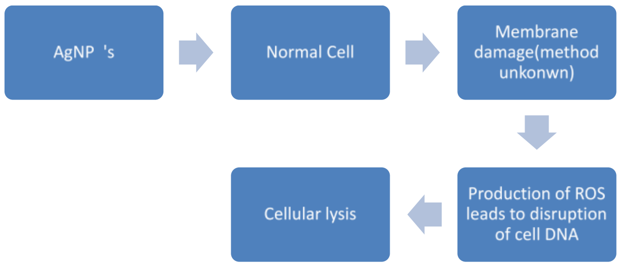

Figure 1. A schematic diagram of AgNPs generating reactive oxygen species in *S. aureus* (adapted from Moritz & Geszke-Moritz, 2013)

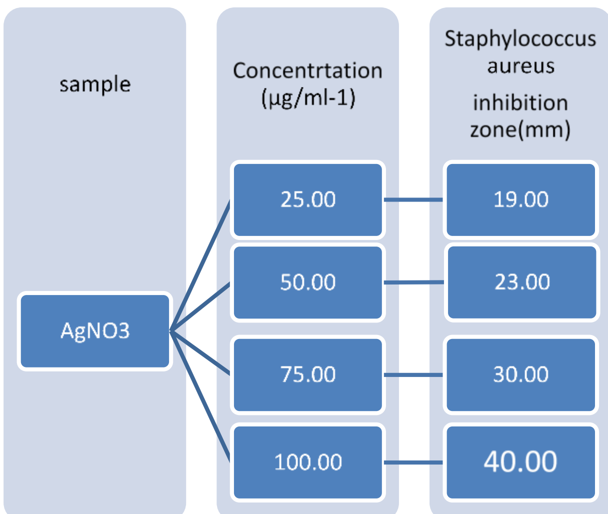

Figure 2. Inhibition zone against *S. aureus* at different $AgNO_3$ concentrations (adapted from Kim et al., 2011).

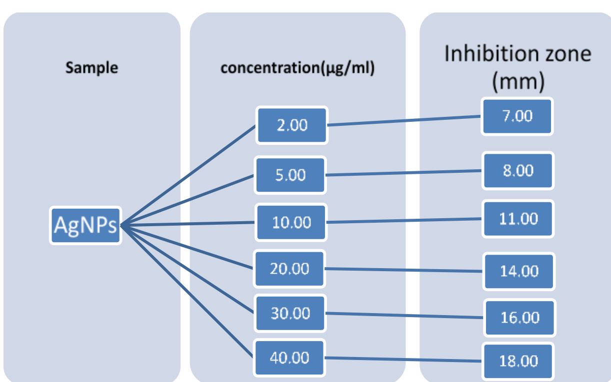

Figure 3. Inhibitory effects of AgNPs against *S. aureus* at different concentrations (adapted from Suganya et al., 2015).

Zia et al. (2018) have reported that exact mechanism of silver nanoparticles against *S. aureus* is still not clear due to presence of double layer peptidoglycan. The other mechanism involves the generation of free radicals by which silver particles kill the bacteria. This reaction takes place at the surface of AgNPs when it is in contact with moisture. During this process, there is production of

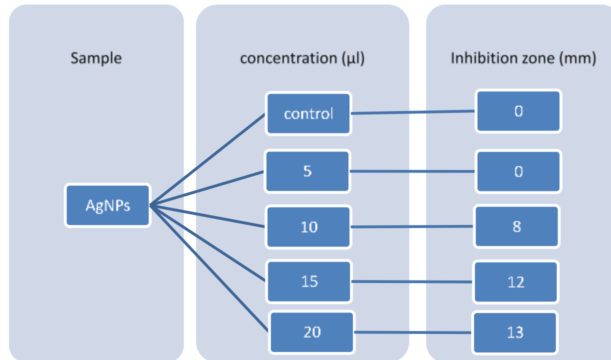

Figure 4. Different AgNPs concentrations showing different inhibitory zones against S. aureus. (adapted from Saravanan et al., 2014).

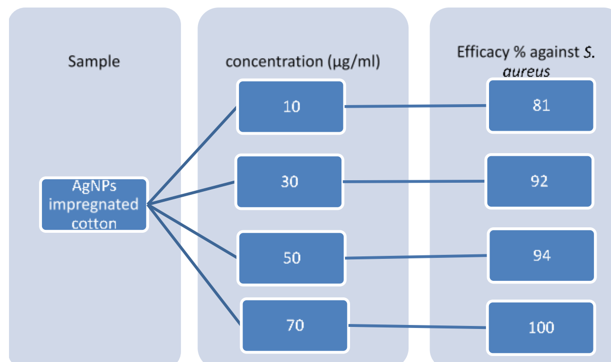

Figure 5. Percent efficacy of AgNPs against S. aureus at different concentrations (adapted form Sung & Lee, 2008).

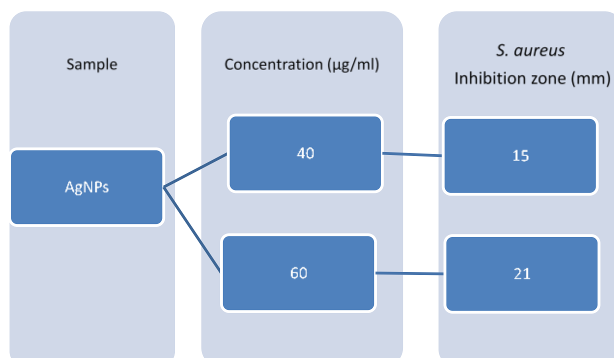

Figure 6. Inhibition zone at two different AgNPs concentrations (adapted from Suganya et al., 2015).

ROS that leads to damage of the outer bacterial membrane, ultimately resulting in bacterial death (Zia et al., 2018). Further studies had reported the effects of AgNPs against multi drug resistance *S. aureus* at different concentrations by using well diffusion method (Figure 4).

Further findings suggested that AgNPs have been used for better treatment to kill extracellular bacteria. AgNPs having 40 nm size have strong antibacterial potential to kill *S. aureus* at low concentration of 56 µM. AgNPs size played an important role to inhibit bacterial activity. The size of 100 nm at high concentration of 927 micro M was able to completely restrict the bacterial activity (Liu et al., 2010; Sarkar et al., 2015). Further experiments were performed to check the efficacy of silver impregnated cotton fabrics against *S. aureus* at different concentrations. As the concentrations were increasing, there was increase in efficacy of silver particles (Figure 5).

Further studies suggested that bio AgNPs have the ability to inhibit *S. aureus* and also to kill pathogenic microorganisms. They observed that silver nanoparticles showed minimum inhibitory concentration of 6.25 µg/ml against *S. aureus*. Both bactericidal and bacteriostatic effects of AgNPs were seen against *S. aureus* (Mukherjee et al., 2001). Biological nanoparticles have better combination with pathogens due to their distinguishing characters such as large volume to surface rates (Xiu et al., 2012). The activity of AgNPs was checked against *S. aureus*. Colony forming units were treated with different AgNPs concentrations (20, 60 and 100 µg/mL). After the treatment, there was a significant reduction in the *S. aureus* colonies. The bactericidal potential of AgNPs increased with increasing the concentrations (Mitra & Das, 2008). Further researchers conducted the experiments at different silver nanoparticles concentrations that exhibited different zones of inhibition in *S. aureus*. This evidence suggested that there is increase in inhibition zone by increasing the AgNPs concentrations (Figure 6).

Kasithevar et al. (2017) conducted the experiments that silver nanoparticles had been synthesized by using extract of CRCP leaves. The developed AgNPs were tested against *S. aureus* isolated from the infections, originated from post-surgery. The AgNPs were highly effective against *S. aureus* and their antimicrobial potential increased with increasing AgNPs concentrations. Kumari et al. (2017) further checked the shape and size dependent antimicrobial potential of AgNPs.

Conclusion: Silver particles have strong antimicrobial potential and can be used as an alternative of antibiotics due to their broad-spectrum nature. Due to their smaller size, these nanoparticles can easily penetrate the bacterial membrane. These particles have better compatibility to inhibit the multidrug resistance *S. aureus* and also to treat the various diseases originating from this bacterium. Size and shape of AgNPs play a vital role in the inhibition of multi drug resistance *S. aureus*. Previous findings suggested that smaller the size of silver particles, greater will be the inhibition zone in *S. aureus*. Spherical shaped and small sized silver nanoparticles exhibit maximum inhibition zone. These particles have better combination with pathogens due to their smaller size. So, it is concluded from all previous findings that AgNPs could be used as powerful weapon against multi drug resistant *S. aureus* and has future perspective against microorganisms.

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