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Review

Updated trends on antimicrobial action of Silver nanoparticles

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Abstract

Silver nanoparticles (AgNPs) are widely spread worldwide from many centuries and are extremely used in industry, cosmetics, food packaging for its proposed antimicrobial activities. Many reports referred to the great value of AgNPs in many faces. This review focused on antimicrobial activities of AgNPs, subjecting briefly to their synthesis, with a special focus on different mechanisms of action and factors affecting these activities as antimicrobial agent.

Key words: Silver nanoparticles, Mechanism, Antimicrobial agent

INTRODUCTION

AgNPs have been used for many centuries as a biocidal in US in 1954 (Nowack et al., 2010). The guide for silver use silver antimicrobial was traditionally from many centuries in ancient Egypt and Rome. Ancient Egyptians were believed in the healing power and anti-microbial effects of silver power by using it prior to antibiotics; also the Phoenicians used the silver vessels for water and wine preservation during their long voyages. The first report for the medical use of silver was as an eye solution in 1884 by the use of 1% ($AgNO_3$) (Russell and Hugo 1994). Recently, silver compounds is recommended topically as antibacterial cream for burn wounds and still used till now (Atiyeh et al., 2007). However, some cytotoxic effects and many limitations to the clinical use of silver materials have been reported (Van De Voorde et al., 2005). In China, AgNPs were used for its antimicrobial action in many places as elevators and railway stations (Sukumaran and Eldho 2012). It has many different forms (organic and inorganic), but the mostly stable one are +0 and +1, although it also exists in (+2, +3) forms (Bogumiła et al., 2013). The forms of AgNPs differs according to sizes (1-100 nm), shape (wires, spheres, triangles, rods), and coatings (polymer, peptide, sugars, citrate) but most forms are derived from Silver nitrate which is the main agent use in the synthesis of AgNPs. Modern advances in nanotechnology, improved the production of silver at nanoscale (Sun et al., 2008); overcoming many cytotoxic limitations with a broad use in many applications including electronic and transparent conductor applications, antimicrobial effects in goods and medical products which leads the growth of the nanosilver market (Williams, 2008). The only fact about Silver is the highly toxicity of it and related compounds against many microorganisms (Zhao and Stevens, 1998). This fact reflects the major roles of AgNPs in medical applications. The most predominant form of silver is silver nitrate, but the nanoparticle form provides major advantage by presence of more surface area for microbe exposure which opens the door about many different uses for its antibacterial action (Sukumaran and Eldho, 2012).

Biological characters of AgNPs

The unique physical, chemical and biological characters of AgNPs attracted the interest compared to usual macro silver (Kim et al., 2007). AgNPs differs completely in their properties from silver as they has higher catalytic activity, higher chemical stability and higher electrical and thermal conductivity (Feng et al., 2008) which makes them of potential value in many applications such as inks, microelectronics, and medical imaging (Matsumura et al., 2003). Besides, exhibiting bactericidal, viricidal and fungicidal activity (Morones *et al., 2005*; Shrivastava *et al., 2007*). The unique antimicrobial Characters of AgNPs

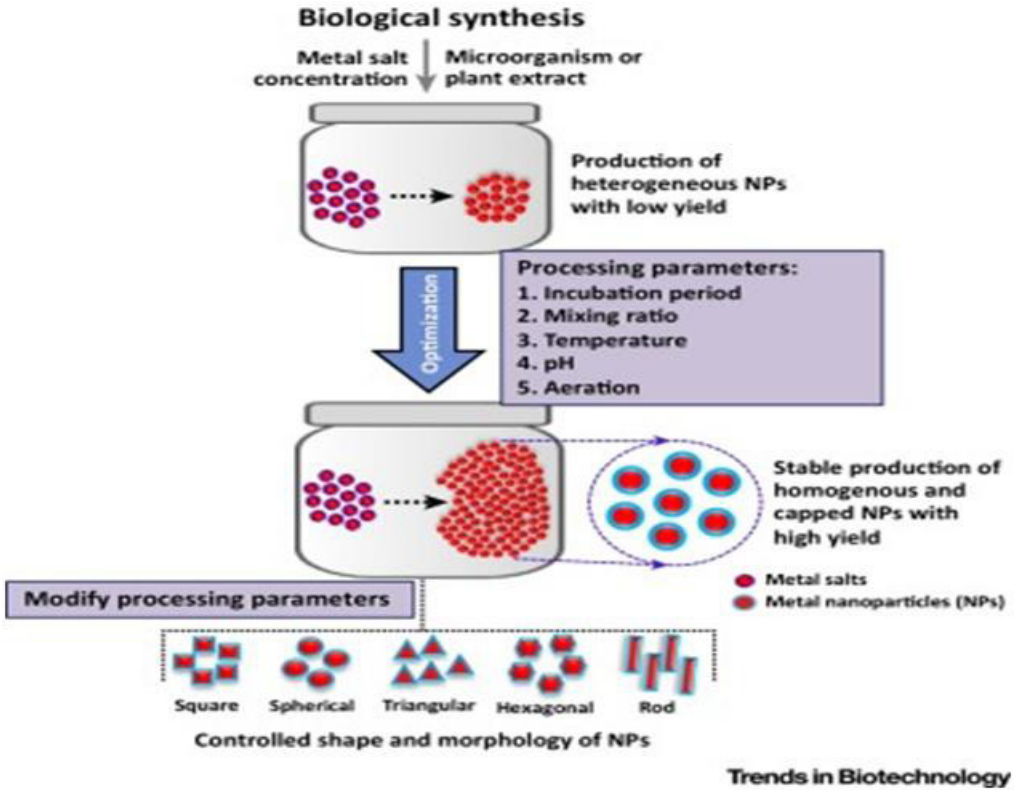

Figure 1. Biological synthesis of AgNPs (Priyanka et al., 2016)

have opened the door for several uses such as clothing manufacturing, food preservation, and water purification (Zhang *et al., 2014*; Chaudhry *et al., 2008*; Benn *and* Westerhoff, *2008*; Manjumeena *et al., 2014*). More importantly, their use in medical industry for their antibacterial, antiviral, antifungal, and anti-inflammatory effects in addition to their ability to enhance wound healing (Zheng et al., 2010; Liu *et al., 2012*).

AgNPs synthesis

Chemical synthesis

The chemical methods is the most commonly used one among the existing methods as it provides an easy and simple way for AgNPs production. There are several methods for chemical synthesis of AgNPs all are based on reduction of silver nitrate firstly by any reducing agent such as ethylene glycol in presence of (PVP) polyvinyl pyrrolidone which produce AgNPs in large quantities (Sun and Xia 2002)or its modification by using a precursor injection technique producing spherical AgNPs with a controllable size (Kim et al., 2006). Generally, three main components are required for chemical synthesis of AgNPs, reducing agents, metal precursors and stabilizing/capping agents (Chen and Zhang, 2012; Dang et al., 2012).

Physical synthesis

The metal NPs can be synthesized physically through evaporation followed by condensation. Briefly, the physical synthesis of AgNPs is depends on use of physical energies such as (thermal, ac power, arc discharge) for production of nano-silver with nearly narrow size distribution, which permits the production of huge amounts of AgNPs in a one process. This method is powerful for production of AgNPs powder. But its major disadvantage is the high costs for investment of equipment (Priyanka et al., 2016).

Biological synthesis

Biologically, AgNPs can be synthesized based on replacement of reducing agent and stabilizer needed in chemical method by biological material such as bacteria, plant, yeasts, fungi, yeasts or algae. This method can provide a wide range of resources. It is an environmentally friendly approach to low-cost technology. It can also accelerate the reduction rate of metal ions in biological agents and improve pressure conditions and ambient temperature (Sintubin *et al.,* 2012). In this way, the main role is played by the negative charge of cell wall of the microorganisms that react electrically with the positive charge of the metal ions and reduce it to NPs

(Thakkar *et al., 2010*), Therefore, incubation of silver ions with microorganisms can generate AgNPs as an internal defense mechanism against metal toxicity. Plant extracts can also be used as reduced agents as reported by Amalad has et al. (2012) (Figure 1).

Antimicrobial Properties of AgNPs

Antibacterial Properties of AgNPs

Antibiotics are the drug of choice in medicine as a standard antimicrobials by targeting specific chemicals present in bacteria not in humans (Van de Belt et al., 2001). This mechanism has two question marks; firstly, decreasing the rang of bacterial species affected by antibiotic due to targeting specific chemicals, the second is developing multidrug resistant bacteria (Ovington, 2004); so developing an alternative antimicrobials is an urgent need. Silver is considered as a great alternative due to its antiseptic properties against broad spectrum of bacteria either gram positive or gram negative as well as vancomycin-resistant strains (Manjumeena *et al.,* 2014, Lok *et al.,* 2007; Ovington, 2004). Moreover, silver-resistant bacteria are rarely developed as this requires three different mutations in one generation at three separate bacterial systems (Silver *et al.,* 2006). Several reports approved the bactericidal effects of AgNPs; Antony et al., 2013 provides evidence for antibacterial effects of AgNPs through in vivo analysis of histological and biochemical parameters on fish models. AgNPs synthesized using Vincarosea leaf extract showed promising inhibition against S. aureus, Lactobacillus, E. coli, and P. fluorescens at 10μL concentration (Kotakadi et al., 2013). The highest inhibition zone (16mm) was obtained for the AgNPs synthesized using Citrus sinensis and Centellaasiatica against Pseudomonas aeruginosa compared to that of AgNPs produced using Syzygiumcumini and Solanumtrilobatum (Logeswari et al., 2013).

Anti-fungal property

The fungicidal effects of AgNPs have not been fully studied yet. In this section we will try to approach the new antifungal properties of AgNPs and its possible mechanisms. There are a lot of antifungal drugs used worldwide but the main disadvantage is the development of fungal resistance by long-term, repetitive administration of standard antifungal drugs especially by the Candida species (Pulit et al., 2013). Therefore, development of new antifungal agents is being persistent need. Many antifungal properties against common fungi are displayed by AgNPs which are presented as a potential effective antifungal agent. A modern study presented that, osmosis membrane in the water purification system can be reversed by coated AgNPs that exhibit a good antifungal activities against many fungal strains such asC. albicans, C. krusei, C. tropicalis and C. glabrata (Manjumeena et al., 2014). Reports of Pulit et al 2013 approved that, AgNPs suspensions created from aqueous extract of raspberry can acts as an effective growth inhibitor against two resistant fungi, *Cladosporiumcladosporioides* and *Aspergillusniger*. Furthermore, the growth of both species can be highly reduced by higher concentration of AgNPs. These results reflect the broad-spectrum antifungal effect of AgNPs. The antifungal activities of AgNPs were examined against Forty four strains of six fungal species by Kim et al. (2008) and the results were demonstrated that, the inhibitory concentration (IC80) was 80% from 1 to 7µg ml^{-1}. The possible supposed mechanisms for this antifungal activity of AgNPs against C. albanicans were explained by disruption of the cell membrane integrity which can inhibit the normal budding process. In another study, Roe *et al* 2008 approved the inhibitory effect of AgNPs against C. albicans which was almost complete when subjected to a plastic catheter coated with Ag-NPs.Additional reports showed the inhibitory effect of AgNPs against yeast growth in the levels below than their cytotoxic limit. Generally, AgNP has a potential biocide effect against many fungal strains and can be used to help the prevention of fungal infections and to protect human health (Figure 2).

Antiviral property

Influenza, Hepatitis, herpes simplex virus (HSV) and human immunodeficiency virus (HIV) and many others can be considered as a life threatening agents. Many vaccines have been developed against most viruses, but till now medicine has not being able to develop a broad-spectrum virus vaccine; and most viruses are developing resistance for current therapy and classic antivirals especially in immune-compromised patients (Gaikwad et al., 2013). In light of this, there has been an urgent need to develop new antivirals against a wide variety of viruses. The antiviral activities of AgNPs are still doubt and many questions of researchers needs answers and few papers are found to investigate the possible effects of AgNPs against viruses. According to several researches, AgNPs can represent an extensive antiviral agent against a wide range of viral strains and are not susceptible to the development of resistance (Ge*et al., 2014*). For example, several studies have shown the antiviral activity of AgNPs against hepatitis B, HSV-1, HSV-2, and HIV-1 (Lara *et al., 2010*; Hu et al., 2014). AgNPs are supposed to target the HSV-1 competing it for its binding receptors via their sulfonate end groups, inhibiting the viral entrance into the cell with subsequent prevention of viral infection (Baram *et al., 2009*). Additionally, a new study showed that AgNPs in a concentration of 100 μg/mL

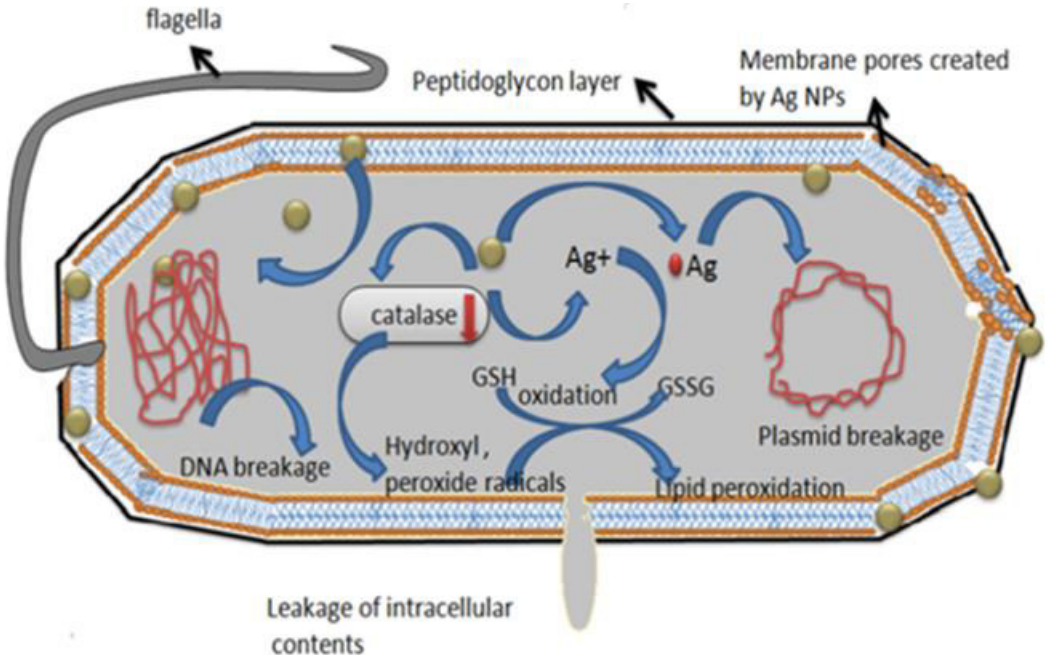

Figure 2. Antimicrobial effect of AgNPs (Sudip et al., 2014)

could completely inhibits replication of HSV-2 when given before or shortly after initial viral exposure, which can reflect its antiviral effect by inhibiting replication in early stages (Hu et al., 2014). In the same way, there has been an evidence of AgNPs antiviral activity against HIV-1 when taken in non-cytotoxic concentrations producing its anti-HIV activity by two theories; the first one by inhibiting the early stage of viral replication (virucidal effect) and the second was by inhibiting the viral entry to the host cell (Lara et al., 2010). Elechiguerra et al. (2005) investigated firstly the interaction between AgNPs and HIV-1, and concluded that, AgNPs produce a size-dependent interaction, (especially between (1–10 nm) and can attach the HIV-1 virus via binding to sulfur group of the glycoprotein residues, and so inhibiting the virus binding to host cells. This mechanism was also approved by Lara et al., 2010. Which bring the virucidal effect of AgNPs back to disruption of the early stage of viral replication, or inhibitory effect of viral entrance to host cell (Figure 3).

Lu et al 2008 investigated the effects of different sizes of AgNPs on HBV using cell line and conducted to that, AgNPs is the only agent that could inhibit its RNA production in vitro. Also, an experiment performed by Sun et al., 2008 to examine the inhibitory effect of conjugated AgNPs with (PVP) against respiratory syncytial virus (RSV) and comparing it with recombinant (RSV) fusion (F) protein. The experimental results showed that PVP-coated AgNPs showed a low toxicity to cells at low concentrations, inhibiting the RSV infection by 44%, which represent a significant reduction when compared to control group. More recently, invitro investigation of the antiviral activity of AgNPs against H1N1 influenza A virus was reported by Xiang et al 2011 Their study revealed that, AgNPs can quickly inhibit H1N1 hemagglutination in chicken RBCs. Inspite of the unclear antiviral mechanism of AgNPs, it is still suggested as a potential veridical agents in the future (Galdiero et al., 2011).

Possible mechanisms for the modus operandi of silver nanoparticles particles

The true about the exact mechanisms of antimicrobial action of AgNPs is not clearly known; however, there are many theories describing the antimicrobial mechanisms of AgNPs on microbes causing microbicidal effect. One theory adopt the ability of AgNPs to attach the bacterial cell wall penetrating and causing conformational changes in the cell membrane affecting its integrity, changing its permeability causing subsequent cell death (Sondi and Salopek-Sondi, 2004). Another mechanism is the free radicals formation by AgNPs which cause cell death by its ability to damage cell membrane, making it porous (Danilcauk et al., 2006; Kim et al., 2007). Mechanistically, the action of silver-based materials depends on the release of silver ions (Ag^{+}) in aqueous solution and its attaching to specific thiol (SH) groups which is the functional groups of multiple enzymes and structural proteins of bacteria, then, generates reactive oxygen species, through the inhibiting the respiratory enzyme casing self-attack of the cell which reflects its antibacterial action (Sanpui, et al., 2008; Morones et al., 2005; Shrivastava et al., 2009). The main disadvantage of non nanoscale silver used in jewelry and silverware is

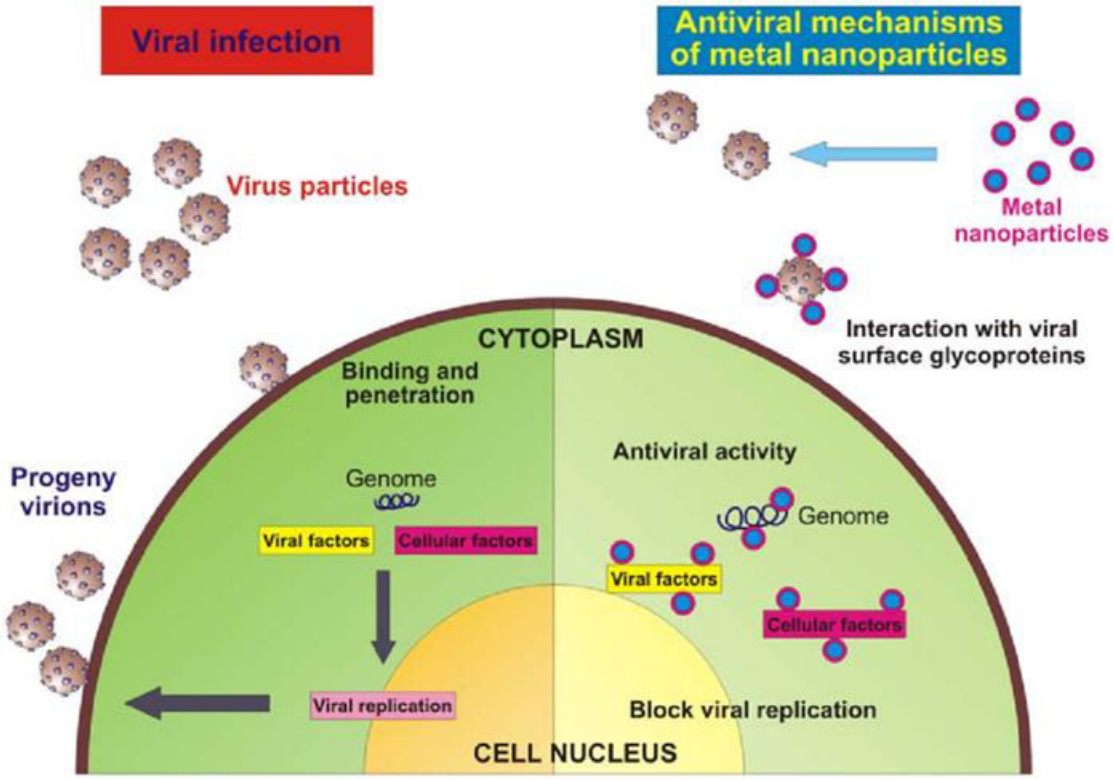

Figure 3. Antiviral mechanism of AgNPs nanoparticles (Stefania et al., 2011)

relatively the insolubility in most fluids, resulting in minimal oxidative Ag^+ release (Ovington, 2004). In contrast, AgNPs provides higher solubility, higher chemical reactivity and a greater active surface due to the greater surface-to-mass ratio (Sotiriou and Pratsinis, 2010; Lok et al., 2007). Sulfur and phosphorus are major components of DNA; at the same time the acidic tendency of silver tends to attack these soft bases causing destruction of DNA, interruption of DNA replication in microbes and DNA damage which would definitely lead to cell death (Hatchett and Henry 1996). Another theory based on modulation of AgNPs to bacterial signal transduction through phosphorylation and dephosphorylation of proteins. AgNPs was found to phosphorylate most of bacterial proteins except tyrosine residues of gram-negative bacteria which showed dephosphorylation properties. This phosphorylation and dephosphorylation of peptides and proteins in bacteria results in inhibition of signal transduction and thus stoppage of bacterial growth (Shrivastava et al., 2007). Choi et al., 2008 represented that AgNPs have higher antibacterial properties than free silver ions (Ag^+) in comparative study of AgNPs, Silver chloride and AgNO3 which implies that, AgNPs have intrinsic antibacterial properties not dependent on the release of silver ions (Ag^+). Lok et al., (2006) supposed one possible mechanism of bactericidal effect of AgNPs is due to its ability to attach the bacterial cell wall and penetrate it, by increasing its permeability leading to cell death. Another possible mechanism supposed by Kim et al., 2007 and explained the antibacterial effect of Ag^+ on the surface of AgNPs through the free radicals formation and the subsequent induction of membrane damage. More recent study suggested by Lee et al., 2014, explained the antibacterial effect of AgNPs, through induction of a bacterial apoptosis-like response through accumulation of reactive oxygen species (ROS) which increases intracellular calcium levels and phosphatidylserine exposure in the outer membrane, all hallmarks of early apoptosis. With DNA damage and disruption of the membrane potential which indicates late apoptosis, in bacterial cells treated with AgNPs. In the light of the above mentioned, it is believed that, AgNPs are thought to interact with the bacterial DNA, the peptidoglycan cell wall and plasma membrane, and the bacterial proteins involved with the electron transport chain to produce their bactericidal effects (Shrivastava et al., 2009; Woo et el., 2008; Yang et al., 2009). Although it is not fully understood which mechanism provides the main antibacterial effect, a combined effect of each mechanism provides broad spectrum antibacterial resistance. (Figure 4)

Factors affecting the antibacterial efficacy of AgNPs

It is noted that, the shape and size of nanosilver affects its antibacterial efficacy. Previous studies by Alt et al.,

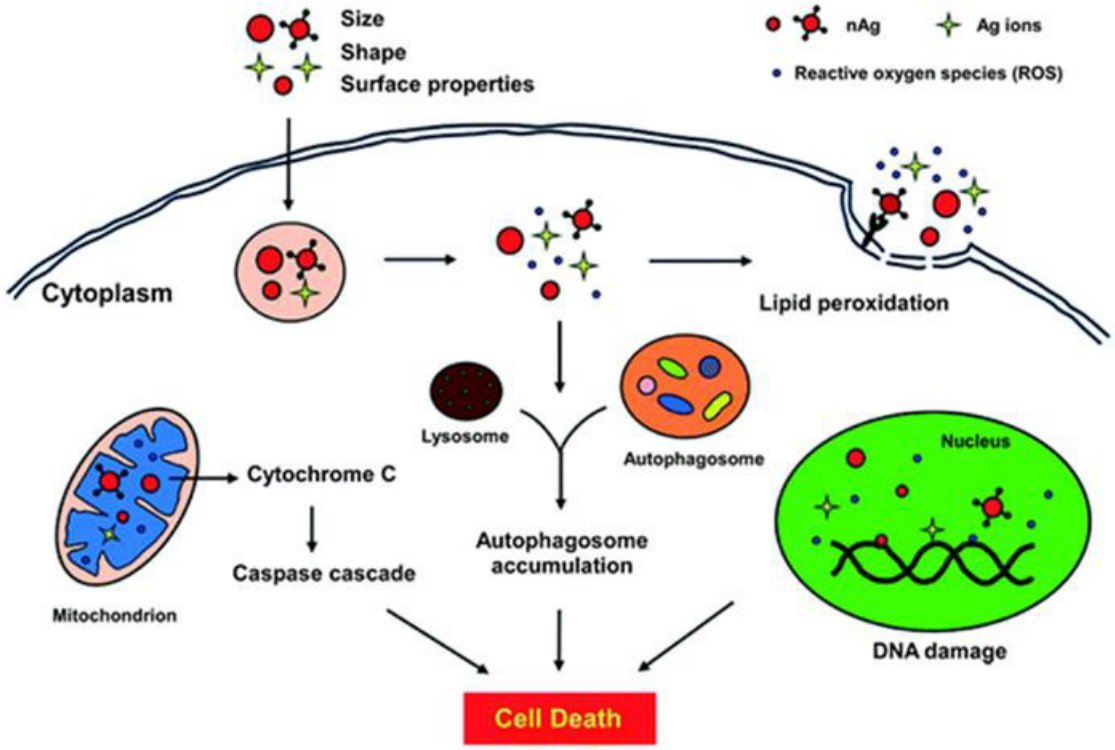

Figure 4. Possible mechanisms of antimicrobial effect of AgNPs (Wang et al., 2015)

2004 demonstrated that 5–50 nm sized AgNPs are bactericidal. Several investigation suggested that, increase the surface area of AgNPs will increase the antibacterial activity (Martinez et al., 2010). In addition, Sadeghi et al. (2012) reported that nanoscale silver plates demonstrated the best antimicrobial activity against *S. aureus* and *E. coli* compared with nano-scale silver rods and particles. Antibacterial activity of nano-silver depends mainly on the surface area of its form, where a larger area is shown. Thus, nanosilver with the greatest surface area exhibits better antibacterial properties at lower concentrations. As discussed, the evidence supporting AgNPs as an effective antimicrobial agent is abundant with AgNPs showing broad-spectrum resistance to bacterial strains such as *S. aureus* (including methicillin resistant strains, known as MRSA), *S. epidermidis* (including methicillin resistant strains, known as MRSE), *E. faecalis, E. faecium, E. coli, P. aeruginosa*, and *K. pneumonia* and even vancomycin-resistant strains (Alt et al., 2004; Lok et al., 2007; Liu et al., 2012; Ovington, 2004).

CONCLUSION

The antimicrobial action of AgNPs is based on either penetration or destruction of cell membrane of bacterial wall or binding to SH groups of main proteins, generating free radial which affect respiratory enzymes and DNA structure causing DNA damage; or affecting the cell signaling through phosphorylation and dephosphory-lation. At the same time antifungal effect depends mainly through the neutralizing effect of silver nanoparticle to the fungal wall, with subsequent destruction of cell wall. The antiviral effect depends mainly on two theories the first one through inhibition of viral attachment to its receptors, the second depends on inhibition of replication in the first stage producing veridical effect.

Finally the use of AgNPs as antimicrobial agent is a unique, as it is difficult to develop resistance as it needs different mutations in different mode of actions at the same time due to different mode of action it depends on. So it can be ideal with more studies.

Future vision

No way that, the use of AgNPsis already established for many biomedical and commercial applications, such as wound dressings, food packaging, and cosmetics industry while many new potential applications are being heavily investigated. AgNPs possess great potential for their anti-inflammatory, antibacterial, antifungal and antiviral properties. However, in spite of the possible mechanisms of the antimicrobial effect explained previously there are many other mechanisms and biological interactions behind these properties are not fully understood. For example, the interaction or the

relation between the size and shape of AgNPs and their biological properties and also the toxicity of it is not fully clear and requires further investigation before widespread medical application can occur.

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