

# Silver nanoparticles for antibacterial and biomedical applications: Synthesis strategies, mechanistic insights, and translational perspectives

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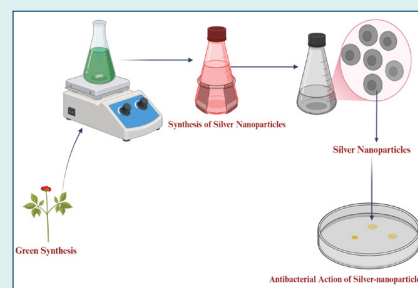
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## Abstract

The potential of silver nanoparticles (AgNPs) as antimicrobial resistance fighters because of their wide-spectrum antibacterial property and multi-functional biomedical applications has made them promising nanomaterials. This review critically analyzes the recent advancements in the synthesis methods of AgNPs such as physical, chemical and green methods and highlights its effect on the physicochemical properties like size, shape, stability and biocompatibility. Unlike the traditional descriptive reviews, the present study also incorporates comparative analyses of synthesis methods based on their scalability, cost, reproducibility and toxicity. In addition, the mechanism of the antibacterial properties of AgNPs, namely the pathways of reactive oxygen species (ROS)-mediated oxidative stress, membrane disruption, inactivation of proteins, and damage to DNA are discussed in detail. Recent studies have provided quantitative information that smaller AgNPs (<10 nm) have much greater antibacterial activity because of their greater surface reactivity and ion release. The review also examines newer biomedical applications such as wound healing, drug delivery, and anti-microbial coatings, and presents the challenges that arise with respect to toxicity, environmental issues, and clinical translation. Overall, this work offers a critical and comprehensive view of AgNPs from a synthesis property activity relationship, suggesting future research on safe and effective biomedical applications of AgNPs.



## Introduction

The antimicrobial activity, high surface reactivity and versatile applicability of the silver nanoparticles (AgNPs) make them a keystone in the nanoscience. There are three major methods for synthesis of AgNPs, called physical, chemical, and green (biological) methods, which have distinct physicochemical properties that allow them to interact better with microbial cells, resulting in enhanced antimicrobial activity against a wide range of pathogens including multidrug-resistant microorganisms.<sup>1</sup> Physical methods use lasers to ablate or evaporate nanoparticles from a bulk material and condense them, but they demand energy input and specialized equipment to achieve high purity nanoparticles. Chemical methods have the advantage of being more controllable to control the particle size and morphology, but they may require toxic reagents and

hazardous byproducts such as those produced by reduction methods using agents like sodium borohydride and citrate. However, green synthesis is getting a lot of interest as an environmentally friendly alternative, and is based on the use of biogenic materials, such as plant extracts, bacteria, fungi, and algae as natural reducing and stabilizing agents. This way, the materials are more biocompatible without negatively affecting the environment. Several mechanisms control the antibacterial activity of AgNPs. They include disruption of bacterial cell membranes, production of reactive oxygen species (ROS), release of silver ions (Ag<sup>+</sup>), interaction with the cells' biomolecules including proteins and DNA, and inhibition of critical metabolic processes. Although much research has been conducted, there are still issues to be addressed to maximize the synthesis and use of AgNPs.<sup>2</sup> Physicochemical characteristics of nanoparticles



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like size, shape, charge on surface, functionalization, etc. have a significant impact on their biological activity, toxicity, and stability. Furthermore, synthesis conditions can differ from one batch to the next, resulting in inconsistencies in reproducibility and scalability, which hinders their clinical translation. Significantly, previous reviews of AgNPs are mostly descriptive and do not critically evaluate synthesis methods or quantitatively correlate with antibacterial activity. Moreover, some physicochemical properties were not correlated with biological activities and translational issues were not addressed, so the present review will focus on the synthesis methods of AgNPs, how they work against bacteria, particularly on structure–activity relationships, quantitative data, and clinical applications.<sup>3</sup> For this review, the literature was gathered from databases like PubMed, Scopus and Web of Science, spanning the years 2020 to 2024.<sup>4</sup> The literature was organized and screened using an AI-assisted tool, which was helpful in improving the efficiency of the literature search, but the data were also critically analyzed and validated by the authors to ensure scientific accuracy and reliability.<sup>5</sup> Although AgNPs possess good antibacterial activity, their clinical translation is limited due to concerns about long-term toxicity, biodistribution, and regulatory approval.<sup>6</sup>

### Synthesis methods

The synthesis of AgNP is a critical step to control their physicochemical properties, which in turn dictates their biological impacts. The size, shape, surface charge, stability and ion release characteristics of the particles are all important parameters that determine the antibacterial activity, which depend directly on the synthesis method.

Hence, rather than a description, the comparative and critical analysis of various synthesis strategies is needed. In general, AgNPs synthesis techniques can be divided into three categories such as chemical, physical, and biological (green) (Fig. 1).<sup>7</sup> Chemical reduction is the most commonly used method for the synthesis of AgNPs because it is simple, scalable, and can be used to produce nanoparticles with controlled size and morphology. In this method, silver salts like silver nitrate are reduced with the use of chemical reducing agents like sodium borohydride, sodium citrate or hydrazine, sometimes with the presence of stabilizing agents that avoid aggregation. Such technique generally results in nanoparticles that are in the range of 5–50 nm with fairly uniform size distribution. Precise control of particle properties can be achieved by the rapid nucleation and growth processes, which is suitable for large-scale production by chemical methods. One major drawback is the use of toxic chemicals, which could cause environmental problems and reduced biocompatibility, which would restrict their direct biomedical application. The AgNPs are generated with top-down approach using physical technique like laser ablation, evaporation–condensation, ball milling etc. without any chemical reagent. These are highly advantageous, especially when purity and contamination need to be as high as possible as required in applications. For instance, in the case of laser ablation, silver particles are formed in a liquid in a controlled fashion from a silver target. Although these benefits are many, physical methods are usually energy intensive, need special equipment, and are high operating cost methods. The green synthesis has become an eco-friendly and sustainable approach to the production of

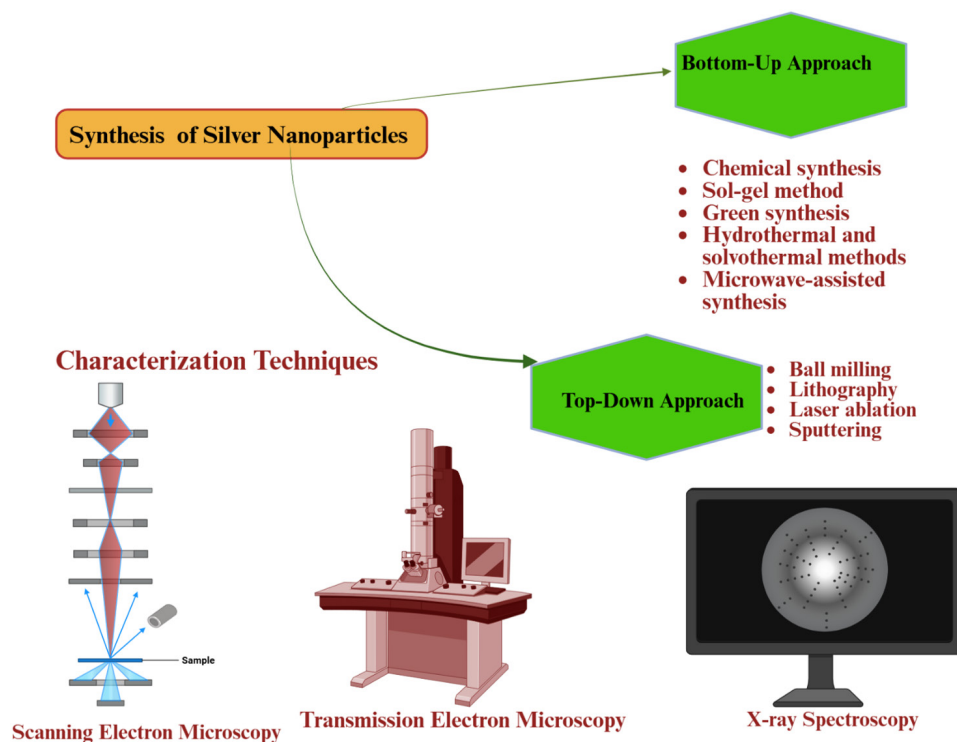


**Fig. 1.** The bottom-up synthesis (chemical synthesis, sol-gel method, green methods (ball milling, lithography, laser ablation and sputtering). The most frequently adopted characterization methods used for AgNPs are SEM, TEM, and X-ray Spectroscopy.

AgNPs. This approach involves the use of natural reducing and stabilizing agents like plant extracts, bacteria, fungi and algae. Flavonoids, phenolics, proteins, are some important phytochemicals that play an important role in reducing silver ions, which in turn stabilizes the nanoparticles. In general, the green synthesized AgNPs have small size of 10-100 nm, low toxicity and high biocompatibility. Furthermore, this approach is environmentally friendly and economical, in compliance with the principles of green chemistry. Variability of the biological sources, however, might result in poor reproducibility and limited control over the particle size and morphology, which is a major challenge. It depends on the purpose of the application and the desired properties of the nanoparticles which are the choice of an appropriate synthesis process. Chemical methods provide excellent control in particle size and high yield, but may be a concern due to toxicity. However, green synthesis is more biocompatible and environmentally friendly but is not always reproducible and variable. Phytochemical methods can give high purity, but are limited by cost and scalability. More importantly, synthesis methods also have an effect on the antibacterial activity. Smaller AgNPs (< 10 nm) generally have higher antibacterial activity because of a higher release of silver ions ( $\text{Ag}^+$ ) and higher surface area, which are produced by more sophisticated physical and chemical methods (Table 1). On the other hand, green synthesized nanoparticles tend to be slightly larger, but have better safety profiles and thus are better suited for biomedical applications.<sup>8</sup>

### Chemical Approach

Chemical synthesis of NPs has been an established method with proven efficacy and reproducibility, and it is a very convenient method because of its ability to control precisely the particle characteristics. Typically, this approach requires the use of metal-based precursors, reducing agents, and stabilizing agents or capping agents. In chemical reduction, the capping agents control the formation of nanoparticles, a technique that is generally used as it leads to the formation of smaller and more uniform particles.<sup>12</sup> It involves two key steps i.e., nucleation and growth in which the silver ions are reduced and collected to form a colloidal suspension of well-dispersed silver nanoparticles. A few factors, such as the kind of precursor, pH, temperature, reducing agent strength, and type of capping materials, have significant effects on the size and growth rate of the initial particle nuclei to achieve uniformly distributed monodispersed particles. It involves such methods as chemical reduction, electrochemical deposition, thermal decomposition, lithography, laser synthesis, and other similar methods. A major benefit of these approaches is the capability to

synthesize highly pure and well-controlled NPs. Stabilizing compounds are used to increase the stability of the nanoparticles, which enhance their uniform dispersion in the liquid and stability against aggregation by being bound to the nanoparticles' surface.<sup>13</sup>

### Chemical reduction

Reduction synthesis is the most popular chemical method on the market because it is simple, scalable and efficient. The choice of the reducing agent plays an important role as it can affect the size, shape and dispersion of the resultant nanoparticles. The capping agent commonly used is polyvinyl pyrrolidone (PVP) which has an electrostatically attractive interaction with silver ions both as a stabilizer and as a size-modulating agent.<sup>14</sup> The reduction of the silver ions to elemental metallic silver is generally done by a variety of reducing agents including elemental hydrogen, sodium borohydride, sodium citrate, ascorbic acid, a variety of block copolymers based upon poly(ethylene glycol), N, N-dimethylformamide (DMF), and compounds involved in the polyol method, which initiate nucleation of the silver and allow growth of the colloidal silver particles. The strength of the reducing agent is more significant in determining the size of the particle smaller the stronger agent and larger the weaker agent. Careful matching of the reducing agent's reactivity (with the silver salt) for its efficient reduction. Optimization of these parameters will be able to control and repeatably produce silver nanoparticles with desired functional properties.<sup>15</sup>

### Sol-gel fabrication

Sol-gel method is an old and widely used technique in the synthesis of nanoparticles. This technique starts with the creation of a stable colloidal system (a "sol") in a liquid media, whether it is water or an organic solvent. The sol is created by methods such as co-precipitation, chemical precipitation, or hydrothermal methods. Chemical precipitation, for example, is a process that requires dissolving a metal salt in a solvent and adding a precipitant to start the process of making nanoparticles. The method of hydrothermal synthesis involves dissolution of the salts of metals in water and heating at a high pressure to facilitate the formation of the sol. The gelation of this sol then occurs by aggregation of sol particles caused by the addition of solvent, chemical cross-linking, or self-assembly due to solvent evaporation. Solvent induced aggregation involves the formation of aggregates when a new solvent is added, and chemical cross-linking consists of binding agents that create a networked gel. The solvent evaporates slowly and slow, allowing the particles to pack together in a more compact gel structure. The overall sol-gel process is

**Table 1.** Comparative analysis of silver nanoparticle synthesis methods

| Method             | Size range (nm) | Yield    | Cost     | Toxicity | Scalability | Advantages                                |
|--------------------|-----------------|----------|----------|----------|-------------|-------------------------------------------|
| Chemical reduction | 5–50            | High     | Moderate | High     | High        | Controlled size, high yield <sup>9</sup>  |
| Physical methods   | 10–100          | Moderate | High     | Low      | Low         | High purity, no chemicals <sup>10</sup>   |
| Green synthesis    | 10–100          | Moderate | Low      | Low      | Moderate    | Eco-friendly, biocompatible <sup>11</sup> |

composed of hydrolysis, polycondensation, ageing, drying and final thermal treatment. Precursor hydrolysis starts when water or alcohol is added, and polycondensation is a process whereby molecules are connected to form a metal oxide matrix and water or alcohol is removed.<sup>16</sup>

### Polyol fabrication

The polyol method is a versatile and efficient means of forming nanoparticles. It includes a polyol that can act as a reducing agent. The reaction is usually carried out with stabilizers or surfactants to affect the shape and size of the particles. The process is performed at high temperatures, usually between 160 °C and 280 °C and can take many minutes to hours. The polyol synthesis method is recognized for the production of nanoparticles with a narrow size distribution, uniform shape, and high purity. Furthermore, the approach can be scaled up and controlled easily, making it applicable for industrial scale reaction.<sup>17</sup>

### Microemulsion method

Another viable route for producing uniform size of silver nanoparticles is by using the microemulsion technique. It uses a "biphasic" system that consists of an organic and an aqueous phase. First, the metal precursor and reducing agents are dissolved in different phases and the reaction takes place at the phase boundaries, sometimes in the presence of a surfactant. They are generally used to create thermodynamically stable microemulsions, typically oil-in-water or water-in-oil types. Surfactants can be either ionic or non-ionic, and play an important part in stabilizing emulsion and controlling the formation of nanoparticles. Usually, one uses cationic surfactants such as PVP or CTAB, anionic ones such as SDS or sodium lauryl sulfate, or non-ionic ones such as Triton X-100. This approach can be used to control the morphology of the particles, but one drawback is that it requires toxic organic solvents. Although this is a disadvantage, the synthesis of

microemulsions may be useful because of their capacity to yield monodisperse nanoparticles. The morphology of the final particles can be controlled by addition rate of precipitating reagent, appropriate reaction time and concentration of precipitating reagent. In some instances, a higher concentration of precipitants can result in longer or 'worm-like' forms of the nanoparticles. Surfactants and stabilizers not only create the environment of the emulsion, but also act as mediators for the transfer of metal clusters from the polar phase to the non-polar phase for the creation of nanoscale particle formation.<sup>18</sup>

### Microwave-assisted synthesis

In advanced synthesis, microwave-assisted synthesis is a good technique for synthesis of AgNPs as compared to the traditional thermal method, which has multiple benefits over the traditional thermal method (Fig. 2). This process always produces nanoparticles of a smaller diameter, with a more uniform size distribution, and more crystallinity. It also decreases the reaction time, energy consumption, and product yield, and also reduces the chance of particle agglomeration and chemical waste. This method is very efficient to shorten the time needed for chemical transformations and organic reactions. In this approach, chemicals like carboxymethyl cellulose sodium (CMCNa) can be used as both the reducing agent and stabilizer; the amount of silver nitrate and the amount of the stabilizer can directly affect the size and stability of the nanoparticles. These particles have been reported to be stable under ambient conditions for long periods. Moreover, AgNPs can be synthesized using well-defined and size, controlled routes such as Micro wave, polyvinylpyrrolidone and seed-mediated synthesis. Starch can also serve as a reducing agent and template, which prevents aggregation and generates about 12 nm sized particles. The integration of the polyol method, via ethylene glycol as both the solvent and a reducing agent, with microwave heating can be

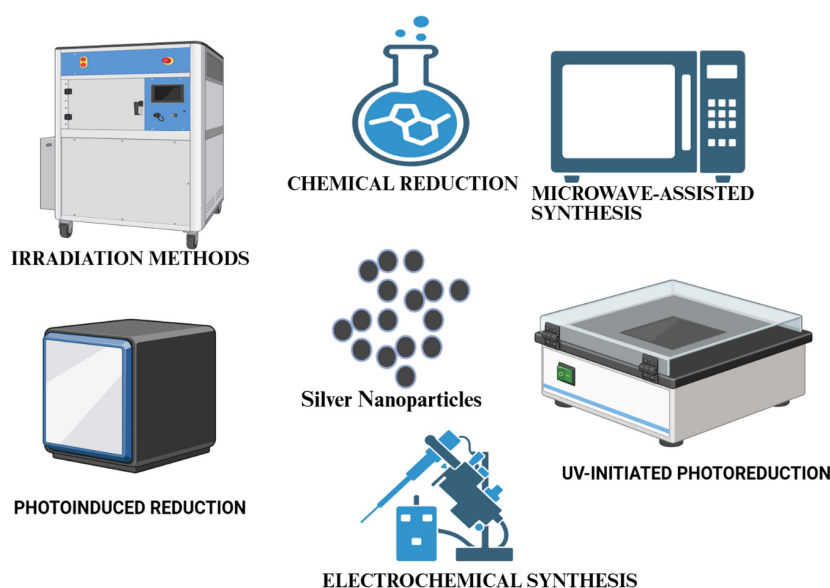


**Fig. 2.** Different preparation techniques of silver nanoparticles such as chemical reduction, microwave-assisted synthesis, irradiation techniques, photoinduced reduction, UV-initiated photoreduction, and electrochemical methods.

utilized to produce more efficient production of silver nano-spheroids. Reactions with silver nitrate and trisodium citrate have been shown to produce silver nanoparticles on a more large scale, and in a more rapid manner, than have been previously demonstrated in the traditional chemical approach. The size and shape of the particles obtained largely depends on the initial state of the silver ions. Under microwave irradiation, silver nanoparticles of different shapes are generated in a few minutes from some solutions containing silver nitrate, ethylene glycol, and polyvinylpyrrolidone. Soluble starch and basic amino acids are used as protective agents to form uniform nanoparticles and minimize the possibility of aggregation.<sup>19</sup>

#### ***Irradiation methods***

Irradiation-based methods are also used to synthesize well-defined and precise silver nanoparticles of well-defined morphologies. Silver salt solutions with surfactant can be controlled by laser irradiation for the formation of nanoparticles. The size of the silver nanoparticles can be controlled by changing the irradiation time and laser power to create particles with a range of sizes, ranging from 5 to 20 nm, which are sufficient for use as photo sensitizing agents. This has been done with various forms of light such as mercury lamps and lasers. It has been investigated that visible light can be used to trigger the formation of nanoparticles by sensitizing dyes, for example, thiophene. Visible light can also be used as a source of energy in the synthesis of nanoparticles, as it has been used to successfully light up complex molecules such as silver-ammonia in ethanol to create stable silver nanoparticles. These techniques provide superior control of shape, size and distribution of nanoparticles by adjusting irradiation parameters.<sup>20</sup>

#### ***UV-initiated photoreduction***

Stabilizers and polymers such as citrate, polyacrylic acid, polyvinylpyrrolidone and collagen have proven to be effective stabilizers for the synthesis of AgNPs using UV-assisted photoreduction. Silver nitrate in a clay matrix is photo-reduced to form stable silver nanoparticles in this approach. The amount of time the particles is exposed to the UV source is important in determining the particle size as well as the distribution. At first, bimodal particle sizes can be seen, but after longer exposure to UV light, the larger clusters will decompose to more uniform and smaller nanoparticles. Moreover, this approach can be applied at room temperature and polyvinyl alcohol (PVA) can be used as a stabilizer to create various silver nanoparticle shapes like nanospheres, nanowires and dendritic structures. The shapes are greatly affected by the concentration of both silver nitrate and PVA. Synthesis of silver nanospheres is carried out by sono-electrochemical methods which involve overlapping ultrasonic and electric pulses. The composition of the electrolyte and the incorporation of complexing agents such as nitrilotriacetate, help to control the morphology and to avoid the agglomeration of the nanoparticles when they are being formed.<sup>21</sup>

#### ***Photoinduced reduction***

However, the synthesis of silver nanoparticles by other methods including photochemical or photocatalytic reduction also has several benefits such as the high spatial resolution, simplicity of operation and improvement of the purity of the obtained nanoparticles. Such a technique is applicable in a wide range of environments, such as polymer films, emulsions, micelles and biological cells. For example, polyelectrolyte capsules can be used as microreactors to synthesize AgNPs with average size of approximately 8 nm. Silver nanospheres can be converted to triangular nanocrystals with tunable edge lengths by dual-beam illumination and by using stabilizers like citrate or poly (styrene sulfonate). Certain organic compounds when exposed to light can efficiently convert silver ions to silver atoms via a radical process; the reaction may be controlled by changing the nature of the substituents, the light source, and the quantum yield. Colloids with different optical and structural properties have been prepared with aqueous solutions of silver nitrate and different wavelength of light from UV to visible light. The UV photoactivation of the surfactant Triton X-100 produces a dual effect as a reducing and stabilizing agent. Moreover, AgNPs have been stabilized with the help of biodegradable polymers like carboxymethylated chitosan, which has led to long term colloidal stability and the size of the fabricated nanoparticles is found to be in the range of 2-8 nm.<sup>22</sup>

#### ***Soft and hard templating methods***

Soft template is a method of assembly of nanoparticles that uses organic molecules, surfactants or block copolymers to promote non-covalent interactions like van der Waals, hydrogen bonding etc. Self-assembly or liquid crystal templating can be used to create mesoporous materials such as MCM-41 or MCM-48 using these soft templates. Resulting depends upon various factors like concentration or chain length of surfactant, composition of precursors and external conditions. The diameter and structure of pores can be fine-tuned by changing the properties of the surfactant or by using pore-expanding agents. There are many cases where this approach has been applied to fabricate a variety of nanostructures such as porous carbon spheres, doped graphene, nanorods and alumina structures. Hard templating, or nanocasting, on the other hand, uses rigid structures like carbon nanotubes, silica, or colloidal crystals to form the shape of the nanoparticles. The precursor is impregnated into the template and after processing, the template is removed, leaving the desired nanostructure. The template is important as it must be easily removable and have the desired porosity and structure. Hard templating can be used to prepare mesoporous replicas, nanowires, 3D frameworks and metal oxide-based nanostructures for various applications.<sup>23</sup>

#### ***Reverse micelle method***

The Reverse Micelle Method is a reliable and flexible technique for preparation of uniform sized and shape nanoparticles. During this process, water-oil emulsions

are created with the water-soluble head of the surfactant on the inside of the emulsion, in a nanosized core. This core is a nanoreactor for the controlled synthesis of NPs.<sup>24</sup>

### **Plasma enhanced chemical vapor deposition**

Plasma-enhanced chemical vapor deposition (PECVD) also known as plasma-assisted CVD is also commonly used for thin film deposition and also for the formation of nanoparticles NPs. This technique can induce chemical reactions in plasma, which enables synthetic production under lower temperatures than in case of traditional CVD. The basic components of a typical PECVD system are: Heating element, an AC or DC power supply, gaseous precursors, and a vacuum processing chamber. The plasma part produces ionized species and reactive intermediates, which further aids in film and NP formation. With low power levels, the plasma activity is also relatively low, resulting in lower reaction rates, and higher particle sizes are formed because there is limited nucleation and the condensation of unreacted species. Decreasing the power, on the other hand, decreases the reactivity and nucleation rate, resulting in larger and fewer particles, and more aggregation. Hard carbon-based NP films containing elements like nitrogen, copper, silver, and titanium have been prepared by adjusting self-bias, doping elements, and using multi-layered metal or carbon structures which have mechanical, optical, and electrical properties that are higher than those of hard carbon-based films. These coatings can be used in solar energy devices, emission components and protective layers. The plasma pre-treatment duration affects the NP density on polymeric substrates as longer plasma pre-treatment tend to decrease the number of NPs, likely due to reduced NP deposition on the substrate. The method has been used to successfully create nanosilica particles with desired anti-reflective properties.<sup>25</sup>

### **Electrochemical synthesis**

The electrochemical approach has the advantage of precise control of the dimensions of AgNPs, which can be achieved by tuning the parameters of electrolysis and the composition of the electrolyte. The silver ions are shuttled across the liquid/liquid interface and reduced using the presence of organic monomers to create silver nano-spheroids. Another method is the growth of the NP within or on modified solid supports, either zeolite films or otherwise, depending on the degree of exchange of silver. Stabilizers such as PVP can be used to synthesize uniform size AgNPs in the range of 1 to 20 nm with narrow size distribution in aqueous environment which reduces the tendency of particle clumping and control the deposition rate. The inclusion of a rotating metal cathode allows for reduced particles to be dispersed throughout the solution and avoid floc formation, creating a more uniform nucleation. The surface-active agents used in the electrolyte further improves particle stability and morphology. This is regarded as a stable and efficient method to synthesize AgNPs of uniform size and shape.<sup>26</sup>

### **Physical approach**

In physical synthesis methods, the synthesis is achieved by mechanical or thermal means, but not by chemical reactions. The following ones involve a top-down process, as the larger particles are reduced to the nanoscale. The process generally entails evaporation of the raw materials, then condensation into fine particles under controlled conditions of temperature and pressure. For instance, thermal decomposition can produce particles with sizes of approximately 9.5 nm, and it is possible to control the heat through the use of compact ceramic heaters and/or to conserve energy. Conventional evaporation-condensation processes are time-consuming, but advances have been made to increase productivity and minimize energy consumption.<sup>27</sup>

### **Ball milling**

High energy mechanical milling method, which dates back several decades, is a method of comminuting bulk material into nanoscale particles by rotating a grinding chamber filled with grinding media. This approach will raise the surface energy of the particles and encourage particle clumping. Depending on the need, various types of milling system setups are available including planetary, vibratory and attritor mills. The ball size, the milling speed, the ambient conditions and the ball to material ratio are all critical variables that affect the NP synthesis. The high-energy ball milling technique is especially effective to prepare particles with diameters of less than 100nm and can be used to produce hard materials and industrial-scale synthesis. Ball milling is an economical method, but it has disadvantages of contamination from grinding tools, long working time and frequent maintenance.<sup>28</sup>

### **Arc discharge method**

The arc discharge method involves a high voltage electric arc between submerged electrodes, vaporizing the metal to form suspended nanoparticles. This fast-moving medium is ideal for creating ionic and metallic silver in solution. The process does not use chemical additives, thus producing nanoparticles with high purity. The produced AgNPs have small and uniform size distribution. The particle size and concentration are strongly influenced by the operational parameters like current intensity, arc time, and electrode gap. The use of multifunctional metallic and ionic silver is useful for the synthesis of silver nanoparticles that can be used in biomedicine, environmental sciences and industries.<sup>29</sup>

### **Evaporation-condensation**

It is a gas phase process that requires precursor materials be placed in a heating chamber where vaporization and condensation occur at ambient pressure to create nanoparticles. Although currently not widely recognized, NP morphology and concentration can be precisely controlled in a controlled environment in a tubular or ceramic based heating system. The process involves three steps: the evaporation of the material, the vapor transport

and the condensation in the form of nanoparticles. This method does not require solvents, but is energy intensive and time-consuming. The characteristics of the particles are affected by the parameters used for the formation of the AgNPs. Different parameters used in the formation of AgNPs (pulse duration, laser wavelength, presence of surfactant) affect the characteristics of the particles. Longer chain alcohols can give more stable and smaller nanoparticles than simpler solvents.<sup>30</sup>

### **Physical deposition**

The physical deposition method (PDM) is a newly developed method known for the excellent uniformity and dimensional accuracy of the AgNPs produced. This approach allows generation of highly dispersed nanoparticles with homogeneous shape, frequently sub-5nm in size. The ability to control parameters like particle diameter, geometry and distribution etc. gives enhanced control of the constituents of the PDM which is of particular interest for different industrial and scientific applications. Innovations in the recent past have proven its ability to generate AgNPs with enhanced structural characteristics, making it a promising method for the engineering of nanomaterials.<sup>31</sup>

### **Melt mixing method**

The melt mixing technique is the mechanical coupling of the polymers to the nanoparticle based fillers by means of processes such as extrusion, kneading or injection molding. It is one of the earliest approaches used to make polymer nanocomposites, and is widely used to impose desired mechanical, electrical or thermal properties. It is used because it is known for its ease of use with existing industrial processes and environmentally friendly characteristics. Such a strategy has proved to be effective to prepare conductive nanocomposites of PP and polypyrrole and the molding into the desired shape. In situ synthesis of hybrid nanoparticles has also been achieved by melting the reactive liquid crystalline polyesters and polymer ionomers that contain sulfonic acid groups. Such reactions are frequently a result of chemistry between the polymers and any metal salts remaining. Melt mixing is widely preferred for the development of advanced nanocomposite materials with desirable performance properties due to its versatility, environment friendly and easy industrial application.<sup>32</sup>

### **Pinning method**

The spinning approach is an efficient method for synthesizing AgNPs, which uses a spinning disc reactor (SDR). The SDR is a rotating disc whose surface and thermal properties can be controlled. In this controlled environment, the nanoparticles are produced in successive stages of aggregation, precipitation, collection and drying. The characteristics of the nanoparticles are determined by various parameters including liquid-to-precursor ratio, positioning of the feed, the speed of rotation of the disc, and the fluid dynamics. This method will be used to ensure uniformity in particle size and distribution and is most

suitable for application of precision nanomaterials with minimal contamination.<sup>33</sup>

### **Inert gas condensation**

Inert gas condensation is a commonly used method for the production of different type of nanoscale materials such as metals, oxides, semiconductors etc. This technique is called vaporisation of metal atoms under controlled pressure in an inert gas (helium, argon, or neon). The metal vapor is quickly cooled, usually by cryogenic methods such as liquid nitrogen, which results in the atoms losing energy, and the nanoparticles recondense from the vapor phase into a range of 2–100nm. The crystallinity and particle dimensions depend on several parameters like type of inert gas, chamber pressure, and evaporation temperature. One of the major benefits of this method is the possibility to create ultra-fine multi-core nanoparticles. But it also needs to be thermo- and pressure-controlled with precision for best results.<sup>34</sup>

### **Ion sputtering**

The ion sputtering process (also called ion beam deposition) was developed in the vacuum environment for the production of single crystalline nanofilms. This technique, which is performed under reduced pressure, exposes a target material to a high electrical potential, causing atoms to be ejected as a result of bombardment by positive ions of an inert gas. The ions formed by the electron collisions in the magnetic field form a plasma that increases the deposition process. The ejected atoms create a vapor which condenses on a substrate to create nanofilms. The method has several benefits such as preserving the intrinsic structure of materials, avoiding high temperature and without the need of expensive precursors. Additionally, it is beneficial for the synthesis of ionic nanoparticles that have programmable sizes and compositions, with less contamination than chemical synthesis methods.<sup>35</sup>

### **Laser pyrolysis**

Advanced nanoparticle fabrication technique involves the use of high intensity CO<sub>2</sub> lasers for activation of gaseous/liquid precursors in Laser Pyrolysis. The reactants are rapidly heated and vaporized by absorbing energy and are then cooled suddenly to form nanoparticles. First the reactants are carried in with a carrier gas or solvent, and then thermally treated and collected from the laser beam. It has been employed to prepare various types of nanomaterials such as metal oxides, ceramics, and composites. It is a process which is known for the production of highly pure and uniform nanoparticles with controlled dimensions. The method uses advanced equipment, but can create very accurate nanostructures for high-end applications in various fields.<sup>36</sup>

### **Biological approach**

The metal salt solution is normally a solution of a metal salt, e.g. silver nitrate, which is allowed to react with a biological extract, causing reduction of the metal ions to the elemental

state by the bio molecules. A typical manifestation of this is a change in colour of the surface caused by surface plasmon resonance. On the other hand, the functional groups (hydroxyl, carboxyl, amine etc) present in the extract, act as stabilizers by forming a protective layer around the nanoparticles, keeping them from aggregation. The particle characteristics (size, morphology, distribution) depend on the nature and concentration of the biological material, pH, temperature and time. It is well known in the field of catalysis and is widely used in other applications such as medicine, environmental remediation, and biosensing, and is also scalable and environmentally compatible.<sup>37</sup>

### ***Plant-mediated synthesis***

Nanoparticle synthesis using plants, known as plant-based nanoparticle synthesis, is a growing green technology. This involves the preparation of plants by cleaning, drying, and grinding the plant material and then extracting it with water, ethanol, or any other solvent used. The resulting filtrate is then added to a solution containing a metal salt under controlled conditions to enable the formation of nanoparticles. The shape, size and surface charge and biological properties of the final product are directly affected by the parameters as extract concentration, temperature, pH and metal precursor amount. This can be used in antibacterial formulations, drug delivery, and biosensors.<sup>38</sup>

### ***Biosynthesis of NPs by bacteria***

Two methods are typically preferred, with the benefit of extracellular synthesis being easier and simpler to use as downstream processing is often straightforward when isolating AgNPs from the reaction mixture. Intracellular synthesis is more complicated and expensive and involves other separation technologies (ultrasonic disruption or chemical extraction).<sup>39</sup> In this case, two alternative pathways are possible: (a) the bioactive bacterial metabolites are released into the surrounding culture media and reduce the silver ions to AgNPs or (b) silver nanoparticles are first produced inside the cells and then excreted to the external culture media.<sup>40</sup> The shapes of these nanoparticles can range from the familiar sphere to the triangle, hexagon, cube and even disk. In some microorganisms intracellular synthesis is also a possibility. This includes the internalization of the silver ions, which then are reduced to nanoparticles inside the cell by the presence of specific enzymes. In other bacteria, synthesis pathways are intra and extracellular. In such cases the silver nanoparticles are synthesized in the internal compartments of the cell and in the external medium. This biosynthesis is of great importance and involves enzymatic activity. The main enzymes that catalyse the reduction of silver ions to elemental silver are nitrate reductases. This reduction takes place with the help of electron transfer from NADH which is mediated by reductases that require NADH. The addition of silver nitrate stimulates the activity of nitrate reductase which consumes electrons from NADH, turning it back into  $\text{NAD}^+$ , and simultaneously reduces

$\text{Ag}^+$  to  $\text{Ag}^0$ . For example, some *Lactobacillus* strains have the ability to produce nitrate reductase at  $\text{pH} > 6$ , which converts the silver ions to nanoparticles. Also, periplasmic and respiratory nitrate reductase participation in these processes was documented. Sugars and proteins found on the cell wall could be found to provide a role of support for silver ion uptake and transformation. Another mechanism proposed is that the silver ions enter the bacterial cell through disrupting the proton gradient and sodium ions are symported with silver ions. The silver binding membrane proteins, when inside, can then further control the ion reduction process, using ATP hydrolysis as driving force. Other enzymes are involved, as well as nitrate reductase. Reduction mechanisms and electron transport chains genes have been found in many bacterial genomes and responsible for biosynthesis of AgNPs by enzymatic or regulatory pathways. The proteins interact with nanoparticles through free amino groups or thiol-containing cysteine residues, or negatively charged groups of carboxylates. The overall negative charge of bacterial cell walls is due to the presence of carboxylate-containing molecules which increases the electrostatic attraction for the silver ion. Other amino acids such as arginine, lysine, glutamic acid, methionine, cysteine and aspartic acid can also be involved in either the reduction or stabilization of the silver ion by acting as catalysts and producing hydroxyl ions. Spectroscopic analysis indicated that the proteins are known to have binding ability to  $\text{Ag}^+$  ions and to encourage the formation of nanoparticles in some bacterial strains. Interestingly, the intracellular synthesis was found to yield higher concentration of protein and the resulting nanoparticles were found to be more negative in zeta potential value and hence more stable. This is probably because variety of biomolecules including lipids, enzymes, peptides, DNA and cofactors exists in the intracellular medium, which is responsible for effective formation and stabilization of nanoparticles. AgNPs synthesized inside the cells are usually more stable against aggregation than the ones synthesized outside. The zeta potential is used for the evaluation of the stability of the nanoparticles in suspension. In general, the values outside the range of  $\pm 30$  mV are considered to be repulsive forces and the dispersion stability is excellent. For instance, intracellular extracts of *Bacillus subtilis* and *Bacillus megaterium* were used to prepare AgNPs, the values of which were determined as Zeta potential about  $-34$  mV which indicates high stability. Bacterial metabolism and the efficiency of nanoparticle synthesis are greatly affected by the environmental conditions. Of these, pH is the most important. The alkaline environment is more conducive to the formation of AgNP, whereas the acidic environment is conducive to aggregation and instability of the particles. In some bacterial species, the initial formation of AgNPs starts at a slightly acidic pH (5–6) and is carried out efficiently in a more alkaline pH.<sup>42</sup> In highly alkaline pH, the reaction takes place at a rapid pace, resulting in the generation of spherical or rod-shaped nanoparticles. On the other hand, a lower pH reduces the reaction rate and causes the particles to take on

a triangular or polygonal shape. Nitrate reductase activity might be increased by increasing the pH, thus speeding up the reduction. Another important factor is temperature. The optimal synthesis temperature is different among the different bacterial species. For example, certain bacteria can produce AgNPs easily at the temperature range of 30 °C–37 °C, and other bacteria like *Kocuria rhizophila* and *Bacillus cereus* can work better at higher temperatures. In general, higher reaction temperatures will produce smaller nanoparticles because the nucleation rates will increase, while lower reaction temperatures may result in larger nanoparticles. The physico-chemical properties of the nanoparticles also depend on the concentration of AgNO<sub>3</sub>. As the concentration of it goes up, the reduction of silver ions also increases. But high doses can produce super-sized aggregates because the growth can be uncontrollable. In different bacterial systems, an optimum concentration has been determined for efficient synthesis. The compositions of growth media also affect the biosynthesis of AgNPs. Cells during stationary growth phases are stressed when the media is rich in nutrients like peptones, salts and yeast extract. When grown under these conditions, bacteria can produce bioactive substances like enzymes, exopolysaccharides, and proteins that may help to reduce metal ions and form nanoparticles.<sup>43</sup>

#### **Biosynthesis of NPs by fungi**

The diversity of enzymes in fungi makes them excellent biocatalysts for the production of nanoparticles. Their cell walls serve as binding centers for metals, and then these metals are reduced to become nucleation centers that then grow into stable NPs. *Verticillium*, *Aspergillus* and *Penicillium* species are famous for their biosynthetic ability of monodispersed metal nanoparticles having antibacterial and cytotoxic properties.<sup>44</sup>

#### **Biosynthesis of NPs by actinomycetes**

Similarly, *actinomycetes* utilize methods to undertake NP generation comparable to that of fungi. *Thermomonospora* species have been shown to synthesize extracellular gold NPs and other strains like *Rhodococcus* and *Streptomyces* species have been used to synthesize antimicrobial silver nanoparticles with a stable morphology.<sup>45</sup>

#### **Biosynthesis of NPs by Algae**

Algae are abundant in their polymers, pigments and proteins and hence these are good sources of bioreducing agents and stabilizers. Both active and inactive algae species can convert the heavy metal ions to nanoparticles. Popular representatives are *Chlorella*, *Nanochloropsis* and *Scenedesmus*, which have been used in the production of catalytically and microbiologically active nanoparticles. The metallic precursors are added to the cultured algal biomass which is then centrifuged and sonicated to isolate and stabilize the internalized nanoparticles. This algal material is dried, then treated with distilled water and filtered to produce a reactive solution. Algal biomass can be sonicated to form a cell-free algal extract for NP formation.<sup>46</sup>

#### **Biosynthesis of NPs by yeast**

Semiconductor nanocrystals can be synthesized by yeasts, especially when they are growing. Protein mediated reduction pathways are used for NP formation by yeast species like *Schizosaccharomyces* species and *Verticillium* species. The morphology and size of particles is affected by environmental parameters such as pH and temperature. Peptide-containing polysaccharides in the extracellular environment enable yeasts to tolerate and sequester metals like cadmium, lead, and mercury, which is the reason for their ability to tolerate metals.<sup>47</sup>

#### **Biosynthesis of NPs by viruses**

The nanoscale size and functionality of capsid proteins (20–500 nm) of viruses enable them to facilitate metal ion reduction. The virus capsids can be used to construct interesting nanoconjugates and nanocomposites for targeted drug delivery and cancer therapy through the process of genetic engineering. For example, bacteriophages are used to synthesize ZnS and CdS NPs, and plant viruses such as TMV are utilized to create biocompatible gold- or silver-based NPs. Nanocarriers containing viruses are believed to be biocompatible and scalable, making them safe, efficient, and adaptable.<sup>48</sup>

#### **Biosynthesis of NPs using biomolecular templates**

The nanomaterials are fabricated using various biomolecules like viruses, nucleic acids, cell membranes and diatoms. The affinity of DNA for the transition metal ions makes it a good choice. It can be used as a template for the nucleation, growth and reduction of metal ions to form gold nanoparticles. The DNA-assisted technique has led to the development of stable assemblies of silver nanoparticles with narrow gaps that are ideal for surface enhanced Raman scattering (SERS) and catalysis of the reductions of nitroaromatic compounds. Continuous gold nanostructures have been synthesized via light-induced or redox-driven processes using DNA, and have properties similar to bulk metals. Seeking inspiration from nature, the membranes obtained from natural sources like latex of *Hevea brasiliensis* have been used as substrate for the thermal reduction of AuNPs. Light can be used to promote reduction and stabilization of AgNPs by microalgae such as *Amphora* species, which utilize components such as fucoxanthin.<sup>49</sup>

#### **Challenges in physical and chemical nanoparticle synthesis**

Although these are effective methods for synthesizing nanoparticles, they have a few major drawbacks. These are high energy requirements, requirement for sophisticated instrumentation and environmental hazards. The use of chemical methods is often very economic and appropriate for scale-up, but is often associated with the use of toxic reducing and stabilizing agents and the generation of hazardous by-products. Such residues are environmentally and biosafe concerns. In contrast, physical methods do not introduce solvent contamination, but are

energy intensive and costly due to the high processing conditions necessary, including high vacuum and high temperatures. Furthermore, methods such as ball milling and lithography typically yield nanoparticles that have broad size distributions and need additional processing steps for uniformity. The additional steps are associated with an additional amount of materials used and energy consumed.<sup>50</sup>

Considering these disadvantages, acquisition of the sustainable synthesis methods of nanoparticles is increasingly gaining importance. The strategies should aim for the least use of hazardous chemicals, reduced energy use and environmentally safe practices. An attractive alternative is the use of bio-genic or green synthesis methods that involve the use of biological systems like microbial cultures, plant extracts, enzymes, and secondary metabolites, which are environmentally friendly. The biosynthetic processes are generally carried out in ambient conditions without the need of severe reaction conditions or chemicals, which makes them desirable for ecological and biomedical applications. Intrinsic proteins, enzymes, and phytochemicals present in biological systems have an intrinsic ability to reduce AND stabilize metal ions and have proven to be very effective at converting metal ions into elemental nanoparticles. Bacterial, fungal and algal organisms can participate in the biological reduction of metal salts. Besides, flavonoids, phenolics and alkaloids are present in plants, which are efficient and natural alternative to the synthetic reagents. This biologically controlled synthesis is not only environmentally friendly, but also economically viable, as it uses abundant and renewable resources. Such properties are particularly valuable in the biomedical field where biocompatibility, purity and reproducibility of nanoparticles are crucial. However, some problems still exist especially in obtaining a narrow particle size distribution, particle shape and uniformity that is normally obtained by chemical and physical methods. Thus, further development is required to optimize biogenic synthesis and to enable its scale-up for commercial production.<sup>51</sup>

#### ***Characterization techniques for metallic nanoparticles***

The characterization of the metallic nanoparticles (MNPs), including those based on silver, is of paramount importance to understand their physicochemical properties, optimize their production process, and optimize their use in specific applications. A range of analytical techniques are used to assess properties such as size, shape, surface structure, composition and stability. The morphological characteristics and internal structures of nanoparticles are determined by using high resolution imaging tools, like SEM and TEM. The important features of SEM and TEM include the fact that SEM provides the detailed surface topology and TEM provides the internal features at the atomic level. X-ray diffraction (XRD) gives essential information about the crystalline structure, lattice parameters and average particle size by analyzing the diffraction pattern that is formed due to X-ray interaction

with atomic planes. Atomic force microscopy (AFM) allows the mapping of the surface in 3D at the nanometric scale, which is useful for the evaluation of surface roughness and interactions at the surface, which are important factors in the research of biocatalysis and drug delivery. Functional groups and molecular bonds on the surface of nanoparticles can be detected using Fourier transform infrared (FTIR) spectroscopy. This is especially true for green-synthesized nanoparticles, where organic residues provide stability and functionality. The optical properties, aggregation behavior and colloidal stability are evaluated by UV-visible spectrophotometry by observing the pattern of surface plasmon resonance. Thermal properties are determined by differential scanning calorimetry (DSC), which measures phase changes (melting and crystallization).<sup>53</sup>

#### ***Polymeric composites and scaffolds in biomedical applications***

Due to their unique structure, polymeric composites and scaffolds are used in biomedical applications. Numerous applications in composite design to wound healing have embraced the use of polymeric systems. Biodegradable synthetic polymers, especially from the polyester family, have attractive features like the ability to be tunable in mechanical properties, controlled degradation rates, and moulded into custom designed scaffold architectures. In 3D printing, polycaprolactone often serves as a material for tissue scaffolds because of its mechanical strength, biodegradability and biocompatibility.<sup>54</sup>

#### ***Phyto-mediated polymeric silver nanocomposites***

The degradation rate of some synthetic polymers can be controlled and the compressive strength is comparable to that of cortical bone, for example, poly (propylene fumarate). Polymeric scaffolds are useful platforms for delivering drugs or cells to wounds, overcoming the limitations of other biomaterials such as low mechanical strength, biodegradability, handling and effectiveness.<sup>55</sup> The advanced composite materials and innovative material fabrication techniques further enhance the functionality of these systems. The types of biodegradable polymer composites are similar to the extracellular matrix (ECM) that helps cells adhere, multiply and differentiate, a critical process of wound healing and skin tissue regeneration.<sup>56</sup>

#### ***The general steps in this green synthesis process include***

a) Preparation of silver salt solution: A silver salt (usually silver nitrate) is added to water to produce a precursor solution of Ag<sup>+</sup> ions. b) Reduction through Biological Agents: A plant extract or microbial culture containing reductive biomolecules is added and the Ag<sup>+</sup> is reduced to metallic silver. c) Stabilization/Capping: These biomolecules also cap the nanoparticles by creating a protective layer, with functional groups of –OH, –COOH or –NH<sub>2</sub> maintaining the colloidal stability of the nanoparticles. d) Nucleation and Growth: When a sufficient concentration of reduced silver is reached, nucleation initiates, forming silver nuclei which aggregate

to form nanoparticles. e) Nanoparticle Formation: Uniform and stable sphere-shaped nanoparticles are formed whose size and shape are dependent on parameters like the pH, temperature, and concentration of the precursor. The last step involves purification and characterization of the obtained nanoparticles using techniques such as centrifugation and analysis tools like FTIR, SEM, TEM, and XRD.<sup>57</sup>

### **Mechanistic insights into the antibacterial properties of AgNPs**

AgNPs demonstrate a comprehensive synergy among their antibacterial, antioxidative, and anti-inflammatory properties, which collectively contribute to enhanced tissue regeneration and wound repair.

### **Antibacterial and antifungal mechanisms**

AgNPs have wide spectrum antimicrobial effects on gram-positive and gram-negative micro-organisms. Their main mode of action is by binding and disrupting the membrane of bacteria, causing cellular contents to leak out and eventually causing cell lysis. They are then taken up by the cell where they disrupt membrane integrity, electrochemical gradients and critical metabolic pathways. Membrane disruption, AgNPs bind to thiol groups present in important proteins, inhibiting their enzymatic activity, and disrupting structural proteins including the peptidoglycan layers and the ribosomes. This causes reduction in energy production; nutrient movement and intracellular signaling. They also interact with nucleic acids, leading to the fragmentation of DNA, and blocking the process of replication and transcription.

The physicochemical properties of AgNPs such as smaller size (< 10 nm), high surface area-to-volume ratio, and positive surface charge plays a significant role in determining the bactericidal potency of AgNPs by increasing the interaction of the cells and the release of ions. Likewise, they show antifungal activity which is related to the interaction with structural polymers in fungal cell walls, such as chitin and  $\beta$ -glucans, causing the cells to become leaky and causing an imbalance of ions and water. AgNPs also cause oxidative stress within fungal cell by producing ROS, which leads to lipid peroxidation, protein damage and DNA fragmentation in fungal cells. AgNPs also disrupt important fungal signalling pathways, including MAPK, decreasing the virulence and making fungi more vulnerable to host defence and antifungal treatment.<sup>58</sup>

### **Antioxidant mechanisms**

AgNPs show significant antioxidative activity, which helps to neutralize the ROS and protects cells. These nanoparticles have the ability to donate electrons or hydrogen atoms to neutralize radicals with the ability to neutralize radicals such as superoxide anions, hydroxyl radicals, and hydrogen peroxide. This decreases lipid peroxidation and prevents oxidative damage of membranes, proteins and nucleic acids. Furthermore, AgNPs increase the expression of the endogenous antioxidant enzymes, including superoxide

dismutase (SOD) and glutathione peroxidase (GPx). These enzymes reduce superoxide radicals and hydrogen peroxide, thereby keeping the redox balance and cell apoptosis levels low. AgNPs have been shown to decrease the levels of lipid peroxidation markers, such as malondialdehyde, which further emphasizes its protective effect against oxidative damage.<sup>59</sup>

### **Anti-inflammatory mechanisms**

AgNPs have significant anti-inflammatory activity due to the regulation of immune response. While inflammation is an essential part of healing, over- or prolonged inflammation compromises tissue repair. AgNPs appear to inhibit the infiltration of immune cells and local tissue damage by downregulating pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, and TNF- $\alpha$ ). At the same time, they boost the creation of anti-inflammatory mediators such as IL-10, which promotes tissue repair.<sup>60</sup>

In addition, AgNPs have been found to suppress the NF- $\kappa$ B and MAPK signaling pathways, which are crucial for inflammatory processes. AgNPs stop these pathways from becoming active, which helps to control the activity of immune cells and the transcription of genes involved in pro-inflammatory responses. Their antioxidant properties also help in combating the inflammation-induced oxidative stress; lipid peroxidation is decreased and mitochondrial function is improved, facilitating damaged tissue regeneration.

In one recent study, green-synthesized AgNPs using *E. camaldulensis* leaf extract and embedded in polymeric matrix made of xanthan gum, hypromellose and sodium carboxymethyl cellulose, exhibited strong antimicrobial activity with microbial growth inhibition of more than 99.9%. These nano-particles also exhibited excellent antioxidant and anti-inflammatory activity, with a strong reduction in nitric oxide production in macrophage cell cultures. Permeation studies showed that it released for 10 hours, and both in-vitro and in-vivo studies showed that it could effectively close the wound within 31 days, which is better than the control that was not treated. The results reveal that the AgNP-polymeric composites synthesized using the green technique can be used in the future as advanced wound dressing materials with multiple therapeutic functions.<sup>61</sup>

### **Effect of metal precursors, reducing agents and stabilizers**

Metal precursors, reducing agents and stabilizers are all factors that affect the structure and properties of the catalysts. Metal sources are key to the structural features, chemical composition and crystallinity of nanomaterials during their fabrication with silver nitrate, silver perchlorate and silver tetrafluoroborate, for example. These precursors determine the initiation and the growth stage of nanoparticles which affects their final properties.<sup>62</sup>

A range of 25 °C to 30 °C is generally considered ideal synthesis conditions and temperatures above 35 °C can affect the growth of the nanoparticles or cause expansion effects that alter the absorption spectrum

towards longer wavelengths. It is generally accepted that higher temperatures speed up the reaction, and lead to larger quantities of nanoparticles and smaller particle sizes, which is revealed by a blue-shift in the spectral data. Experimental research with natural extracts also has emphasized the need to select appropriate metal salts, reducing agents and stabilizers for optimal synthesis. The absorption peak around 400 nm has been observed under favorable conditions, which signifies that the formation of silver nanoparticles has been accomplished successfully. Synthesis parameters, such as the precursor type, reducing and capping agents, solution pH, and temperature, have been shown to significantly affect the yield, uniformity, and stability of nanoparticles synthesized using different plant-based methods.<sup>63</sup>

### **Capping agents in silver nanoparticle synthesis**

Capping agents play an important role in the process of generation and stabilization of AgNPs. They perform many important tasks like avoiding the aggregation of nanoparticles and maintaining them in a stable state. Using biogenic synthesis method implies the use of many biomolecules responsible for the intensification of biological action of AgNPs. Such phenomena can mostly be explained by the existence of biological “corona” made up of biomolecules from the source plant or organism. The corona normally consists of proteins, enzymes, and phytochemicals that provide simple and efficient interaction with microbial cells, increasing the chances that the nanoparticles will attach to the cells and penetrate through the membrane, thus enhancing their antibacterial impact, reducing cytotoxicity to mammalian cells, and improving the dispersibility of nanoparticles in biological media. These molecules can attach to the nanoparticle surface due to different types of interactions, such as ionic, Van der Waals or covalent bonds, which affect the size and shape of AgNPs. There are also proteins that help stabilize nanoparticles in the biological medium, since they can bind to the surface of AgNPs and act like natural capping agents by preventing agglomeration. Such process is very common in AgNPs that are made using microorganisms, algae, fungi or plants. There are proteins that can serve like mediators increasing biocompatibility and antimicrobial activity of AgNPs, since those proteins can make an interaction with other biomolecules. There are also enzymes such

as glucanases and chitinases that are found in fungi, performing the dual action of reducing and stabilizing AgNPs formation. In case of plants synthesis of AgNPs, there are also proteins that can be used for stabilization purposes. Peptides containing functional groups like carboxyls, produced in the process of protein digestion, can perform like surfactants when forming corona layers surrounding and stabilizing AgNPs. Exopolysaccharides can have negatively charged groups such as hydroxyl, carboxyl and amide that can interact with silver ions and be used as capping agents. Monosaccharides such as glucose, fucose, mannose and galactose can contribute to providing stability of nanoparticles in some bacterial systems and plants.<sup>65</sup> These polysaccharides could stabilize nanoparticles but also perform antimicrobial and anti-biofilm functions, which can be traced in certain natural extracts. Flavonoids well-known for their broad-spectrum antimicrobial activity are involved in the process of producing AgNPs by breaking bacterial membranes, blocking necessary enzymes and stopping lipid biosynthesis. Their amide groups or hydroxyl groups could have potent capacity for binding metals and enable the enclosing of nanoparticles creating a shell preventing aggregation. Such polyphenolic compounds as catechins, gallic acid derivatives, and others could also be used in the AgNPs capping processes in various plants (Table 2).

Another group of polyphenols, tannins also acts as capping agents. Their hydrophilic functional groups make hydrogen bonding possible and hydrophobic parts can interact with the lipids of membranes and proteins of microbial cells. The growth of microorganisms is inhibited by these organic compounds through the alteration of the permeability of cellular membranes and the process of protein synthesis, allowing them to act as effective capping agents and antimicrobial materials. Certain kinds of alkaloids may have some kind of antibacterial effect and can act as capping agents for nanoparticles. These nitrogen-containing elements might serve as antibiotic enhancers. It has been proved that the alkaloids belonging to some extracts of plants can be utilized for binding to silver nanoparticles AgNPs, making them more stable and increasing their antibacterial power. There are other types of natural biomolecules like saponins and terpenoids which may also be used for capping purposes too. Saponins can help nanoparticles create a protective coating due to

**Table 2.** Synthesis Methods, Precursors, and Capping Agents for Metallic Nanoparticles

| Synthesis method          | Precursor                    | Capping agent                                 |
|---------------------------|------------------------------|-----------------------------------------------|
| Chemical route            | Copper nitrate               | Hydrazine hydrate <sup>66</sup>               |
| Wet chemical method       | Platinum 2,4-pentantedionate | Oley-Lamine and oleic acid <sup>66</sup>      |
| hydrothermal              | Silver nitrate               | Nanocellulose <sup>67</sup>                   |
| Microwave-assisted method | Silver nitrate               | Lignin <sup>68,69</sup>                       |
| Conventional method       | Silver Nitrate               | Trisodium citrate <sup>70</sup>               |
| Spray pyrolysis           | Gold chloride                | Polyvinylpyrrolidone <sup>70</sup>            |
| Hydrothermal synthesis    | Gold chloride                | Cetyltrimethylammonium chloride <sup>72</sup> |
| Green synthesis           | Copper Sulfate               | Rhus Coriaria <sup>73</sup>                   |

their antimicrobial properties and potential synergy with antibiotics. Terpenoids stick to Ag nanoparticles initially in their oxidized form or later in their natural state on the surface of silver due to carbonyl or aromatic bindings. These organic agents preserve the stability of nanoparticles by ensuring proper interaction on their surface due to the inclusion of  $\pi$ -electrons or some other reactive groups.<sup>74</sup>

### ***Mechanisms of Antibacterial Action of Silver Nanoparticles***

*Lipopolysaccharides* present in gram-negative bacteria are known to possibly enhance AgNPs binding due to their negative charge, which in turn may facilitate bactericidal activity.<sup>75</sup> After attachment, AgNPs might serve as local storage compartments for silver ions which would diffuse slowly into cells thus leading to cell lysis. Interestingly, some categories of bacteria can experience significant changes in their ultrastructure post-exposure to AgNPs including formation of pits and leaking of cytoplasm. In particular, very small nanoparticles, including those lower than 10 nm are found to be more effective, due to their surface area, which makes it easier for them to penetrate inside a cell and destruct its internal structures. AgNPs exposure changes the membrane potential of bacteria and zeta potential demonstrating the failure of their membranes. There are significant morphological shifts caused by AgNPs, including the thinning of the membrane, shrinkage, and folding of membranes observed in various bacteria. The impact of AgNPs on the enzymes containing thiol groups located in the respiratory chain alter the process of metabolism and energy creation. Due to the high affinity of silver to sulfur and phosphorus, the membrane proteins and enzymes involved in cellular metabolism may be compromised. The process of cellular uptake of AgNPs involves a binding stage, which is followed by the endocytosis process. After entering the inside of the cell, the silver nanoparticles alter the permeability of the membranes and the process of functioning of cellular components, thus contributing to ROS formation. The aforementioned ROS, such as  $H_2O_2$ ,  $O_2$ , and hydroxyl radicals, will result in oxidative stress that is damaging to critical biomolecules and causing death of cells. Increased levels of reactive oxygen species result in damages to DNA and proteins. AgNP-mediated oxidative stress has been known to cause DNA damage characterized by strand breaks, conformational alteration, and disturbance in DNA replication and transcription process. Smaller AgNPs are more effective at producing reactive oxygen species which not only cause lipid peroxidation but also lead to membrane damage. Silver ions could attach to DNA which changes its structure and inhibits its replication as well as diminishes efficiency of transcription. AgNPs could interrupt ribosome function by binding to the ribosomal 30S subunit which would impede the process of protein synthesis. Their affinity for ribosomes and enzymes hinders the cell walls maintenance, DNA replication, and energy metabolism. Proteomic studies reveal that exposure of AgNPs leads to modulation of proteins responsible for transport mechanisms, oxidative stress response, and membrane

stabilization. On the contrary, proteins involved in DNA and RNA metabolism, as well as ribosomal proteins show downregulation. At the same time, there is a possibility that nanoparticles produced by biological means create similar effects. For example, silver nanoparticles manufactured by means of lignin or microorganisms impact the expression of genes responsible for membrane transport, formation of biofilms, and stress response mechanisms.<sup>76</sup> AgNPs are also effective in boosting protein leakage due to their influence on enzymatic activity and sugar metabolism, which causes sugar metabolism to be affected particularly in gram positive organisms such as *S. aureus* in contrast to Gram negative bacteria. AgNPs have an even greater effect on enzyme functioning, causing enzymes responsible for energy production to be inhibited. Inhibiting ATP generating enzymes results in decreased energy production as well as decreased survival of bacteria. The capping agents involved in green synthesis enhance the antimicrobial effect achieved from the action of AgNPs. Their properties involve blocking of protein synthesis in bacteria of destabilization of membrane proteins through binding. Their actions work in synergy with AgNPs in a "poisoned arrow" manner since the nanoparticles will not only be used as a carrier for the compounds but also constitute their antimicrobial action by the bioactive compounds that are attached (Fig. 3). The action of AgNPs can be summarized as follows such as adhesion, invasion of the bacterial cell membrane, interaction with proteins, DNA, and other intracellular components, induction of oxidative stress, intervention on processes of respiration and energy metabolism, and interference with signaling processes.<sup>77</sup>

### ***Toxicity***

Before the use of AgNPs in medicine, it is crucial to understand their toxicity (Fig. 4). It is necessary to assess the risks and benefits of the use of AgNPs as therapeutic agents in order to evaluate their effect on human health.<sup>78</sup>

### ***In vitro studies***

Many studies have utilized nanotechnology to examine the impact of AgNPs on human cells in vitro. These studies are important in clarifying AgNPs' therapeutic potentials and risks related to their medical uses. Usually, alongside studies on the anticancer properties of AgNPs, which is extremely promising. The cytotoxicity of AgNPs depends on many factors such as size, shape, and stabilizing agents used in their synthesis. For example, smaller nanoparticles demonstrate much higher toxicity than larger ones regarding lung monocytes, macrophages, and epithelial cells. Spherical nanoparticles are the most toxic of all shapes when comparing the same shapes together. Capping agent can either enhance or lower toxicity, depending on their chemical properties. Fibroblasts are used for tests of AgNP toxicity. Some AgNPs from certain plants produced in increasing concentrations did virtually not influence normal mouse fibroblast cell lines viability.<sup>79</sup> AgNPs derived from other plant sources have not displayed damaging effects on fibroblast cell lines. Interestingly, the

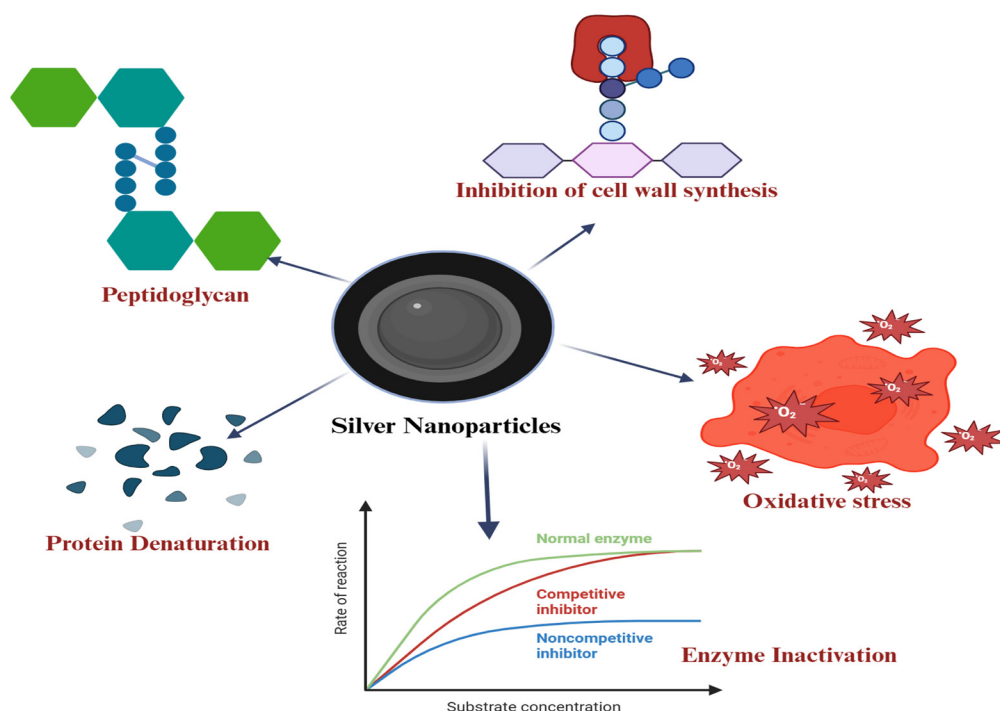


**Fig. 3.** AgNPs exert their antimicrobial effects through multiple pathways, including disruption of peptidoglycan structure, inhibition of cell wall synthesis, induction of oxidative stress via ROS generation, protein denaturation, and enzyme inactivation through competitive and noncompetitive inhibition, ultimately impairing bacterial survival and function.

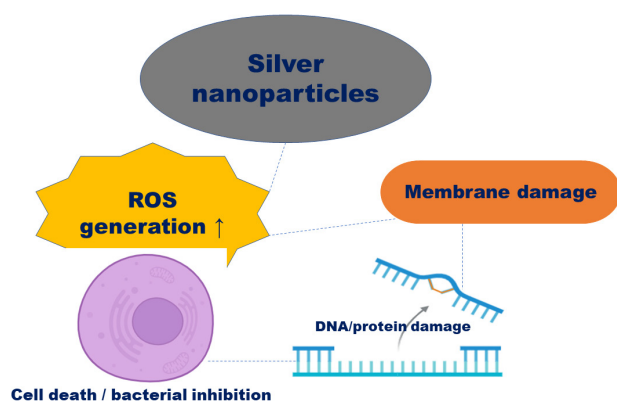


**Fig. 4.** Schematic representation of in vitro antibacterial and cytotoxic mechanisms of AgNPs.

AgNPs from certain plant sources are much more toxic to cancer cell lines than to normal fibroblasts given that the bioactive material within them contributes to their better effectiveness and lower toxicity. For instance, nanoparticles produced from sources like black tea, that contain a lot of polyphenols and antioxidants have low viability on normal cells but high viability on cancerous cells. Blood-based human cell lines are used in some studies to analyze possible immunotoxicity. AgNPs have decreased the viability of white blood cells in some cases following a dose-dependent pattern. They show different impacts in terms of the viability of mononuclear cells in the peripheral blood. Such findings can be useful for predicting possible immune reactions and response of AgNPs towards immune cells. Despite some plant-based AgNPs having low toxicity at certain concentrations and high viability to cells, red blood cells are also used for toxicity testing.<sup>80</sup> AgNPs synthesized

from biological sources exhibit a very low level of hemolytic activity at low concentrations and may sometimes even stabilize membranes of RBCs. It is observed that the degree of hemolysis rises with the increase of the concentration of the NPs and smaller particles are more liable to cause hemolysis than big ones. Some green AgNPs exhibit low toxicity to RBCs suggesting that they might be safe in pharmacological applications. In addition, studies conducted on macrophages show that biosynthesized NPs might be advantageous as they have lower cytotoxicity and do not compromise immune responses. In addition, low concentrations of AgNPs are shown to possess anticoagulant and thrombolytic abilities they prevent blood cells from aggregating and, thus, decrease the likelihood of formation of blood clots. Although there are many studies that indicate biocompatibility of AgNPs there are some findings that exhibit that they might have a negative effect. Thus, it is possible for AgNPs to accumulate in the organs such as the liver and the kidneys and cause oxidative stress, genetic damage, and inflammation. It may lead to a variety of health problems. The toxicity of AgNPs is mostly caused by their ability to generate free radicals that harm cellular. The degree of impact is determined by the quantity and size of the nanoparticles and therefore, smaller nanoparticles cause higher damage. Additional research has shown that AgNPs have a toxic effect on liver and lung tissues depending on the dose of nanoparticles. Some nanoparticles produced from the plants were discovered to have a negative impact not only on the tumor cells but also on the fibroblasts, such as the range of application is very limited. A number of experiments involving the use of fish as the biological objects revealed that AgNPs get deposited

in many organs, namely gills, brain, and also intestines and liver leading to changes in tissues and structures at the cellular level. Similar changes can be observed through fish cell lines in which AgNPs resulted in rounding and localization of cell shapes. The mechanisms of toxicity in such cases are explained by the impact of biological compounds used for stabilization in the process of synthesis. However, despite all these possible disadvantages of AgNPs that are biologically produced, they usually possess lower toxicity and higher effectiveness compared to the AgNPs produced through chemical means.

### *In vivo studies*

Studies on animal models have indicated that some AgNPs synthesized through green methods could be capable of providing certain protective benefits (Fig. 5). AgNPs originating from certain mangrove species were found to be able to protect mouse liver from the damage inflicted by chemicals. Other studies reported the antioxidant as well as the protective effects on the liver and kidneys of rodents treated with AgNPs after the toxins were induced since the biochemical parameters were restored to normal values. Some types of AgNPs displayed no negative effects on the indices of the kidney functions and structure in rats. The parameters important for kidneys and liver functioning, such as creatinine and albumin levels along with liver enzyme levels, remained normal. In certain cases, the application of AgNPs was able to prevent the liver damage caused by rather toxic drugs like paracetamol. Another instance of application of AgNPs from certain sources showed that AgNPs were able to heal wounds contaminated with antibiotics resistant bacteria.<sup>81</sup>

### *Applications of silver nanoparticles*

In addition to antibacterial functions, AgNPs manufactured using green technology are found in various fields of medicine, ecology, and industry (Fig. 6). In medical applications, they are used in bandages to promote healing by preventing intimate contact with microorganisms and encouraging the healing process. Getting incorporated into gels, creams, or coatings for medical devices, AgNPs minimize the probability of infections transmitted in hospitals. Additionally, AgNPs are studied for usage in anticancer technology, drug delivery systems, and bioimaging because of their peculiar

optical performance and the ability to be modified with drugs. In terms of ecology, AgNPs perform an essential function in water treatment technologies, as they kill pathogenic microorganisms and decompose organic compounds in water. AgNPs are also applied in food industry, where they enter film-based packaging materials and prolong food preservation periods due to microbial impact. AgNPs are used to improve signal transduction in biosensors for detecting various biological substances. In the textile industry, manufacturers use AgNPs to improve the production of textiles with a wide range of anti-odour and antimicrobial properties. Moreover, AgNPs have been used in sectors like solar panels and catalysis, demonstrating their multi-purpose applicability even beyond the medical area. Additionally, the green synthesis method has contributed to the fight against environmental problems by ensuring cost-effectiveness, scalability of production, and compatibility of the technology with safety requirements. The flexibility of the size, shape, and surface chemistry of AgNPs are a result of the variation of synthesis conditions.<sup>82</sup>

### *Wound healing applications*

Silver nanoparticles are a widely used material in the field of wound dressings because of their significant antimicrobial properties and anti-inflammatory effects. Use of silver nanoparticles interspersed in dressings inhibits microorganisms, preventing the infection process.<sup>83</sup>

### *Antimicrobial coatings and medical devices*

AgNPs are often included in coatings for medical implements such as surgical tools, implants, and catheters in order to obstruct the creation of biofilms and the development of hospital infections. Besides, the consistent emission of silver ions guarantees long-lasting protection against microbes.<sup>84</sup>

### *Drug delivery systems*

AgNPs are promising nanocarriers that can improve drug stability, facilitate targeted delivery, and enhance therapeutic effectiveness. Functionalized AgNPs can be effective in drug delivery of antibiotics, anticancer drugs, and biomolecules as well.<sup>85</sup>

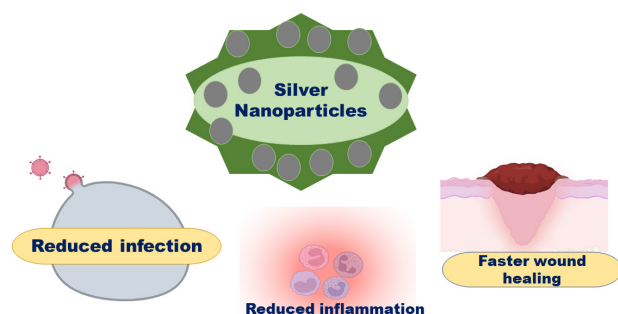


**Fig. 5.** Summary of in vivo therapeutic effects of AgNPs, demonstrating enhanced wound healing and antimicrobial efficacy.

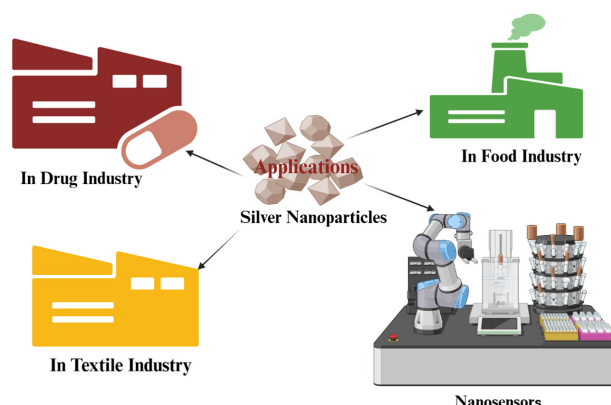


**Fig. 6.** Applications of silver nanoparticles across multiple sectors.

### Anti-inflammatory and antioxidant applications

Besides their antimicrobial properties, AgNPs also have anti-inflammatory properties as they modulate the production of cytokines while reducing oxidative stress. This quality enables their use in managing inflammation-related diseases and supporting the healing processes.<sup>86</sup> Medical applications of AgNPs related to their antimicrobial activity and safety are presented in Table 3.

### Clinical translation of silver nanoparticles

AgNPs have shown great antibacterial as well as biomedical potential, yet the safety of the compound is still a serious problem for its use in clinics (Table 4). The toxicity profile of AgNPs is related to many factors such as size, form, charge, concentration, duration of exposure and the method of administration. All these factors must be considered to make the proper combination of effectiveness and safety of the particle. AgNPs exert their cytotoxic effects due to oxidative stress and mitochondrial dysfunction as well as damage of the cellular membrane. Reactive oxygen species produced by AgNPs cause lipid peroxidation, protein denaturation, and DNA damage thus leading to apoptosis or necrosis. Smaller nanoparticles have bigger cytotoxicity because of their surface and because of their ability to penetrate the cells easily. AgNPs violate cellular signaling pathways and lead to violation of normal processes at the cellular level.<sup>92</sup> Local toxicity of AgNPs typically manifests itself at the application sites via such effects as irritation or inflammation of the skin in topical applications. On the other hand, systemic toxicity occurs when AgNPs are injected into the bloodstream and reach different organs. Their accumulation in such organs might cause toxicity and oxidative damage, as well as disrupt the function of the organ. The level of systemic toxicity depends on factors such as AgNPs dosage, frequency of exposure, and their characteristics. The need for optimizing AgNPs dosing is evident because of possible negative consequences. The frequent application of AgNPs makes one worry about their potential impact on the environment. Their discharge into water resources may harm aquatic animals by causing oxidative stress. The same applies to the need for further studies of the issues of long-term stability and bioaccumulation of AgNPs in ecosystems.<sup>93</sup>

### Challenges in clinical translation

There are various obstacles to overcome despite encouraging outcomes obtained in vitro and in vivo in clinical applications of AgNPs, such as different methods

of synthesizing and limited evidence regarding their long-term safety.<sup>98</sup> Furthermore, the existence of two distinct environments laboratory and biological add to the complexity of predicting any outcomes in the practical use of AgNPs. Finally, the regulatory approval of AgNPs also poses a serious problem, because toxicological studies and quality control are compulsory prior to their clinical application.<sup>99</sup>

In 2016, one of the first phase I/II clinical investigations was carried out by Lawson Health Research Institute in Canada, using AgNP hydrosols as a treatment for patients with refractory chronic rhinosinusitis. The randomized-crossover trial consisted of 20 individuals treated with either AgNPs formulations or saline rinses. Topical silver therapy was used as a commercially available AgNP hydrosol preparation. The results showed that there were no significant adverse effects and tolerability of the treatment was good, but there was no convincing clinical benefit compared with saline treatment. Therefore, the topical administration of AgNP was deemed safe, but not more effective than conventional nasal irrigation treatments.<sup>100</sup>

### Future perspectives

Further studies should be conducted in order to develop more effective and safer formulations of AgNPs, which can be done through surface modification, use of delivery systems of nanoparticles and controlled release. Application of advanced technologies such as creation of nanocarriers and designs that rely on artificial intelligence may make the treatment more effective while reducing toxic effects.<sup>101</sup>

### Conclusion

This review stands out from the previous works because it involves a comparative examination of various bio-synthesis strategies, incorporates quantitative biological data, and discusses the translational issues. Whereas ordinary reviews provide a description of the existing works, this one gives a clear link between the properties of the nanoparticles and their biological efficiency. The use of nanotechnology for exploiting the biological potential of the organisms including bacteria, fungi, and plants is a green way to synthesize AgNPs. However, while the shape and size of nanoparticles is of utter importance and still remains difficult to regulate, replacing toxic chemicals with eco-friendly natural compounds is considered to be a sustainable approach. The efficacy of AgNPs as antimicrobial agents has been established in numerous

**Table 3.** Biomedical applications of silver nanoparticles

| Application       | Mechanism                         | Benefit                            |
|-------------------|-----------------------------------|------------------------------------|
| Wound healing     | Antibacterial + anti-inflammatory | Faster healing <sup>87</sup>       |
| Coatings          | Biofilm inhibition                | Infection prevention <sup>88</sup> |
| Drug delivery     | Targeted delivery                 | Increased efficacy <sup>89</sup>   |
| Anti-inflammatory | Cytokine modulation               | Reduced inflammation <sup>90</sup> |
| Diagnostics       | Optical properties                | Sensitive detection <sup>91</sup>  |

**Table 4.** Summary of toxicity and clinical considerations of AgNPs

| Parameter               | Observation             | Impact                           |
|-------------------------|-------------------------|----------------------------------|
| Size (< 10 nm)          | High cellular uptake    | Increased toxicity <sup>94</sup> |
| Dose (High)             | ROS generation          | Cell damage <sup>2</sup>         |
| Exposure (Long-term)    | Organ accumulation      | Systemic toxicity <sup>95</sup>  |
| Surface coating         | Reduced reactivity      | Improved safety <sup>96</sup>    |
| Route of administration | Determines distribution | Affects toxicity <sup>97</sup>   |

studies. AgNPs are capable of treatment of infections and inhibiting biofouling and activities of quorum sensing. The mechanism of action of AgNPs is cellular and molecular including their adhesion to bacteria's membranes, penetration into cells, disturbance of their vital cellular systems, and generation of reactive oxygen species creating a lethal effect. AgNPs are different from common antibiotics since they can penetrate and disrupt biofilms, which are otherwise resistant to conventional antibiotics. Additionally, they have shown higher anti-biofilm activity compared to many other types of metallic nanoparticles, such as gold nanoparticles. When used in various materials such as cotton or polyester, AgNPs can prevent the development of bacteria, thus opening the way for the use of such materials for medical clothing or coatings of medical devices in order to minimize the risk of infection. Furthermore, AgNPs can interfere with bacterial signaling, thus broadening their bactericidal capabilities. Apart from shape, size, and concentration, the type of capping agent contributes to the efficacy of AgNPs. Many bioactive compounds of plant origin, such as phenolic compounds, flavonoids, alkaloids, glycosides, and terpenoids, have been proven to be responsible for this activity. These natural agents have been used in traditional medicine for a long time, which then inspired the creation of advanced nanomedicine. AgNPs derived from isolated bioactive agents show excellent activity against multi-resistant pathogenic bacteria. AgNPs derived from signal agents can lead to disruption of quorum sensing and biofilm formation in resistant strains of bacteria. The same effect has been caused by plant-based. However, the ability of AgNPs to provide therapeutic benefits needs to be proportionate to their toxicity potential. While the majority of research findings indicate that AgNPs show compatibility with human and animal cells, other studies show potential dangers that include accumulation in important organs as well as allergic reactions and nanoparticle aggregation. The safety issues raised above need thorough study to guarantee the safety of AgNPs' clinical usage. Despite the above difficulties, bioderived AgNPs which are non-toxic and are biocompatible and have different functions can definitely lead to the invention of alternative medicines.

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None to declare.

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The authors declare that ChatGPT (OpenAI; <https://chat.openai.com/>) assisted tools were used solely for language refinement, grammar correction, and improvement of clarity and readability of the manuscript. The AI tools did not generate scientific content, interpret data, perform analyses, or influence the study design, results, or conclusions. All intellectual content, data interpretation, and scientific responsibility remain entirely with the authors.

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