



Review on Synthesis, Characterization and Medical Applications of Silver Nanoparticles

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Review Article

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Abstract

Silver has been used extensively from last 5000 years for its antibacterial nature. Silver is preferred as nanoparticle for the reason that it has antibacterial property and nontoxic to human beings. Silver nanoparticle (AgNP) demand is rising quickly across a wide range of industries, including healthcare, pharmaceutical, food, consumer goods, cosmetics, and medicine. It has been utilised for a variety of purposes, including antibacterial qualities, medicine, the food industry, wound dressing, orthopaedics, diagnostics, and as an anticancer agent. These nanoparticles may be used for a variety of applications since they are unique in nature and have the ability to alter their physical, chemical, and biological properties. There are three different ways to prepare AgNPs: physical, chemical, and biological. The biological approach is the most straightforward, environmentally friendly, marketable, and one-step of the three techniques. It also requires no harmful chemicals, high temperatures, pressures, or forces. Prior to using nanoparticles for any purpose, such as medicine, human welfare, or the healthcare sector, it is crucial to characterise the manufactured particles in order to determine any potential safety concerns. Applications for AgNPs include antifungal, anticancer, antibacterial, and more.

Keywords: Nanoparticles; Silver nanoparticles; Nanomedicine; Green synthesis

Abbreviations

HBV: Hepatitis B Virus; ROS: Reactive Oxygen Species; SEM: Scanning Electron Microscopy; TEM: Transmission Electron Microscopy; XPS: Xray Photoelectron Spectroscopy; AFM: Atomic Force Microscopy; FTIS: Fourier Transform Infrared Spectroscopy; DLS: Dynamic Light Scattering.

Introduction

The science of nanotechnology has made incredible strides in recent years, transforming a number of sectors and creating new opportunities for scientific research [1-5]. Since ancient times, silver has been utilized as an antibacterial. For instance, the Phoenicians preserved wine and water on

their lengthy journeys by using silver pots. Furthermore, Before antibiotics, silver compounds were utilised to prevent wound infection since the ancient Egyptians thought that silver powder had antidisease and healing benefits [6]. To prevent food, wine and water from spoiling, the ancient Greeks and Romans stored them in cutlery. Silver preparations were utilised by Hippocrates to encourage wound healing and cure ulcers. Additionally, silver nitrate was used to sterilise instruments and treat wounds. Sims employed thin silver wires to stitch the vesicovaginal fistulas brought on by delivery in 1852, greatly reducing infection. Silver formulations for wound infection and burn treatment were created around the start of the 1800s [7].

Due to their distinct physicochemical characteristics as compared to their bulk forms, nanomaterials (1–100 nm materials) have garnered a lot of attention in recent decades in a variety of sectors, including biology, catalysis, energy storage, and sensing. Particular attention has been paid to silver nanoparticles (AgNPs), particularly in the field of biomedicine. AgNPs are well known for their potent and wide-ranging antibacterial and anticancer properties. Additional biological functions of AgNPs have also been investigated, such as improving vaccine immunogenicity, boosting bone mending and wound repair, and having anti-diabetic properties. Understanding AgNPs' biological processes and possible cytotoxicity can help improve their use in medicine [8,9].

The synthesis of AgNPs with regulated size and form is the subject of several investigations, and several specialised synthetic techniques, such as physical, chemical, and biological approaches, have been established. Mechanical and vapor-based processes are the two main categories into which physical procedures fall. Milling, pyrolysis, and spark discharge are examples of conventional physical techniques.

AgNPs with a consistent size distribution and excellent purity may be produced by physical synthesis. The most widely utilised technique for producing AgNPs is chemical synthesis. Nucleation and growth are the two stages of this process, which entails converting silver ions to silver atoms. AgNPs with regulated size and form may be produced by adjusting the nucleation growth rate [10,11]. In addition to reducing agents, stabilising agents and capping agents are crucial for producing AgNPs with a consistent size distribution and strong dispersion stability. AgNPs may also be synthesised synergistically by external energy sources such light, heat, sound, and microwaves. Despite the widespread use of chemical synthesis techniques for AgNPs, greater focus has to be placed on the toxicity and pollution that chemicals generate. When it comes to AgNPs, the biological process is more cost-effective and environmentally friendly than the physical and

chemical approaches. Both plant components, such as bark, peel, callus, leaves, flower, fruit, stem, seed, and rhizome, as well as microorganisms, such as bacteria, fungus, and algae, are extensively utilised in biological synthesis [12]. Enzymes, alkaloids, phenolic compounds, and terpenoids are among the many organics found in plant and microbe extracts that may be useful for reducing silver salts. It is also possible to employ some of these organic materials as capping agents and stabilisers. Among the many techniques, the additions listed might have an impact on AgNPs' future medicinal uses [13].

AgNPs are known to have broad-spectrum and strong antimicrobial activity; even at very low concentrations, they can effectively eradicate a wide range of pathogens [14]. These include (i) bacteria, including *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus*; (ii) fungi, including *Candida albicans* and *Aspergillus niger*; and (iii) viruses, including HIV and Hepatitis B virus (HBV). Additionally, some research has demonstrated the nematocidal and anthelmintic properties of AgNPs. AgNPs' antibacterial actions are well acknowledged to involve DNA damage, reactive oxygen species (ROS) production, and bacterial cell wall destruction [15]. Rare AgNPs resistance in bacteria is seen, in contrast to the danger of antibiotic resistance, which might restrict medicinal uses [16]. This might be explained by AgNPs' numerous antibacterial mechanisms acting simultaneously.

Numerous studies utilising AgNPs conducted in recent years provide sufficient proof of the promising medical uses of silver nanoparticles. However, we should exercise caution when using AgNPs due to their possible toxicity to cell lines *in vitro* and to humans *in vivo*. This serves as a reminder to conduct additional research in order to produce safe, biocompatible AgNP-containing agents. In order to comprehend the profound implications for medicine, this paper offers an objective evaluation of the applications of AgNPs and potential toxicities.

Characterization of Silver Nanoparticles

Monitoring the physicochemical characteristics of each nanoparticle is crucial for both safety and effectiveness. Therefore, representation is crucial for verifying or assessing the functional characteristics and attributes of synthesized nanoparticles. As previously mentioned, a variety of techniques are employed to characterize these nanoparticles. These techniques include XRD, FTIR, DLS, UV-Vis spectroscopy, TEM, SEM, and XPS. Schematic representation of different characterization techniques used for silver nanoparticles are shown in Figure 1. By using these techniques, we can ascertain different characteristics of synthesized nanoparticles [17]. Some of the important characterization techniques are explained in detail below.

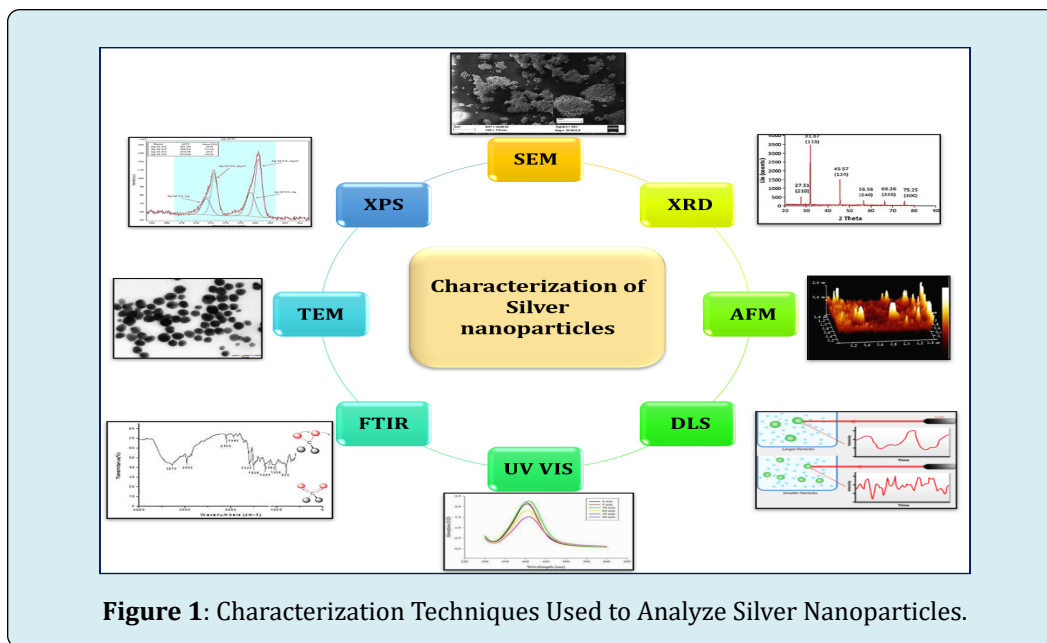


Figure 1: Characterization Techniques Used to Analyze Silver Nanoparticles.

Scanning Electron Microscopy (SEM):

Many methods, including many electron microscopy techniques, are employed to get a deeper understanding of nanotechnology and nanosciences. SEM is one among them. SEM is a method that is mostly used to ascertain the particle's morphology. Since SEM is a surface imaging technique, we may use it to ascertain the sizes of particles, their distribution, surface morphology, and the forms of nanomaterials. SEM allows us to determine the morphology of particles, after which we can either manually count the number of particles or use another piece of software to construct a histogram. Along with EDX, SEM is used to analyse the chemical composition and identify the shape of silver powder. SEM has the advantage of allowing us to detect particle purity and the degree of aggregation, but it also has the drawback of not allowing us to identify the interior structure of the particle [18].

Transmission Electron Microscopy (TEM):

One of the most widely used and significant techniques for characterising particles is TEM. We can determine the quantitative dimensions of particle size, particle size distribution, and particle morphological characteristics using this TEM approach. The TEM's magnification may be ascertained in part by the distance between the objective lens and the specimen as well as the distance between the objective lens and the picture plane. Compared to SEM, TEM can offer superior resolution and analysis.

SEM's drawbacks include the need for a high vacuum rate, the need for a very thin sample slice, and occasionally the time commitment [19].

X-Ray Photoelectron Spectroscopy (XPS):

Using the X-Ray Photoelectron Spectroscopy (XPS) approach, empirical formulas are estimated. Electron Spectroscopy for Chemical Analysis (ESCA) is another term for XPS. This method is typically applied in high vacuum settings. We can locate, recognise, and describe the distinct groupings of macromolecules' aromatic rings using this XPS approach. Additionally, it facilitates access to data on qualitative, quantitative, and speciation issues pertaining to the sensor's surface [20].

Atomic Force Microscopy (AFM):

AFM is frequently used to determine the dispersion and aggregation of nanomaterials. In addition to their dimensions, form, and structure, there are three more scanning modes and these three modes are referred to as intermittent sample contact mode, non-contact mode, and contact mode. AFM can be used to characterise the communication of nanomaterials with their lipid bilayer support, something that other electron microscopy techniques are unable to accomplish. AFM's drawback is that the size of the cantilever causes the sample's lateral dimensions to be overestimated; therefore, considerably more care should be taken to eliminate inaccuracy [21].

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR makes it feasible to identify minute variations in absorbance, up to 10^{-3} , which eventually aids in the execution of difference spectroscopy, which in turn aids in identifying small combination bands of functionally dynamic

residues that remain after the large absorption bands of proteins. We may ascertain whether biomolecules are involved in the creation of nanoparticles using this approach, which also offers accuracy and reproducibility. In addition, FTIR is a non-invasive method. Other applications for FTIR include the verification of functional compounds grafted onto carbon nanotubes, silver and graphene nanoparticles, gold, and silver. Strong data, quick data collection, a high signal-to-noise ratio, and less sample heat up are all possible with FTIR. All things considered, FTIR is a straightforward, precise, useful, economical, and non-invasive method for verifying the role of biomolecules [22].

Dynamic Light Scattering (DLS):

Physiochemical parameters or the assessment of synthesised nanoparticles are crucial parameters for the research of biological activities utilising the radiation scattering approach. A particle DLS may be used to determine sizes ranging from submicron to one nanometre. Since this DLS can identify particles between 2 and 500 nm, it can also easily identify smaller particles. This technique essentially relies on how light and particles interact. It is the method most frequently used to measure the size and dispersion of particles. DLS primarily uses Rayleigh scattering from light from nanoparticles on the edge to measure light that is scattered from a laser that can pass through a colloid.

The hydrodynamic particle size can then be determined by analysing the modulation of the scattered light force that is acting as a function of time. It has been noticed that the size obtained by DLS is superior to that obtained from TEM; this could be because of Brownian Motion. The main application of this technique is the measurement of particle size in aqueous solution [23].

Green Synthesis of Silver nanoparticles

There are numerous potential uses for green nanoparticle production in the biomedical and environmental domains. Reducing the use of hazardous chemicals is the main goal of green synthesis. For example, using organic materials like plants is generally safe. Reducers and capping agents are also found in plants.

Silver metal ion solution and a reducing biological agent are essential for the environmentally friendly synthesis of silver nanoparticles. Silver ion reduction and stabilisation by a fusion of biomolecules like polysaccharides, vitamins, amino acids, proteins, saponins, alkaloids, terpenes, and phenolics is the simplest and least expensive way to produce silver nanoparticles. Numerous medicinal plants, including *Saccharum officinarum*, *Helianthus annuus*, *Cinamomum camphora*, *Oryza sativa*, *Aloe vera*, *Capsicum*

annuum, *Medicago sativa*, *Zea mays*, and *Magnolia Kobus*, can provide silver nanoparticles for use in biological and pharmacological applications [24-26].

Protein treatments, which are environmentally beneficial microorganisms present in plant extract, serve as reducing and capping agents in the manufacture of stable and shape-controlled silver nanoparticles. High microbiological activity against both Gram-positive and Gram-negative bacteria was seen when polymers and surfactants were used to modify silver nanoparticles.

A methanolic extract of the *Eucalyptus hybrida* plant has been used by some researchers to create silver nanoparticles. Boiling 10 g of *Nelumbo lucifera* leaves in 100 ml of distilled water yields silver nanoparticles. A 1 mM aqueous solution of AgNO₃ (88 ml) was added to the filtrate solution (12 ml), and it was then allowed to sit at room temperature in the dark. The creation of silver nanoparticles (AgNPs) was identified as a solution with a brownish yellow hue [27,28].

Hibiscus rosa sinensis leaf extract was added to 25 millilitres of a 10⁻³ M AgNO₃ solution, and the mixture was vigorously agitated for five minutes. The light brown silver nanoparticles underwent a 30-minute temperature decrease at 300 K. Additionally, silver nanoparticles were created by heating a 10⁻³ M aqueous solution of AgNO₃ (20 ml) with 5 ml of *Jatropha curcas* seed extract for 15 minutes at 80°C. The solution turned reddish in the interim, signifying the creation of silver nanoparticles [29,30].

The use of plants to produce silver nanoparticles has gained popularity recently due to its quick, environmentally benign, non-toxic, and cost-effective protocol, which offers a one-step method for the biosynthetic process. The simplest and least expensive method of producing silver nanoparticles is by combining biomolecules (such as proteins, amino acids, polysaccharides, terpenes, alkaloids, phenolics, saponins, and vitamins) that are already present in plant extracts. Figure 2 shows the schematic representation of silver nanoparticles by plant extract and AgNO₃.

The main benefits of employing plant extracts for the synthesis of silver nanoparticles are their accessibility, safety, and generally nontoxic nature, as well as their wide range of metabolites that can help reduce silver ions and their speed of synthesis compared to bacteria. Plant-assisted reduction is the primary mechanism taken into consideration for this process due to photochemicals.

The silver nanoparticles are stabilised by the comparatively large concentrations of steroids, saponins, carbohydrates, and flavonoids, which function as reducing agents and phytoconstituents as capping agents.

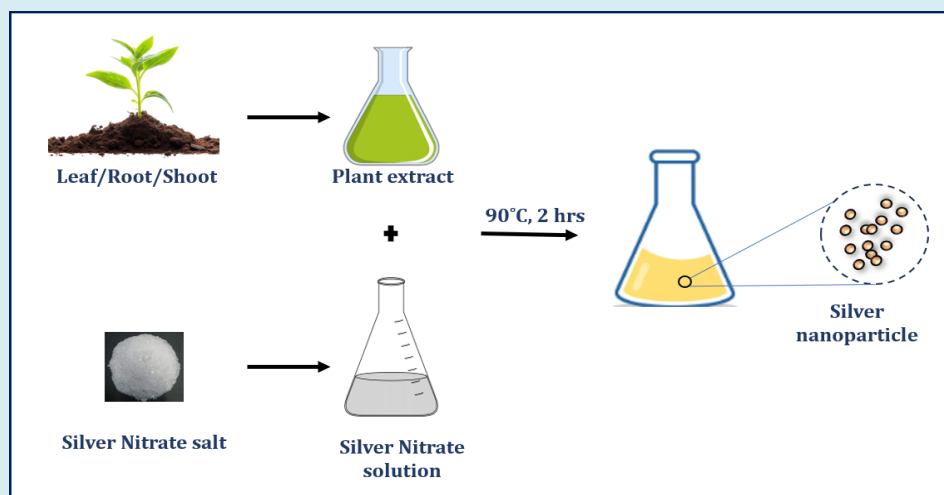


Figure 2: Green Synthesis of Silver Nanoparticles by Plant Extract and AgNO_3 (Reproduced from Pal G, et al. [31].

Medical Applications of Silver Nanoparticles

Because of their special qualities, silver nanoparticles are used in many aspects of daily life. Their use in fabric cleansers, household cleaning agents, antireflection coatings, to enhance heat transmission from solar energy collectors to their fuel tanks, to create high-performance delicate electronics, and in hundreds of other applications are just a few examples. Even though all of these are significant uses for silver nanoparticles, the medical industry may be the one that needs them the most. The general medical applications of silver nanoparticles are shown in Figure 3. The general characteristic of nanoparticles is that their small size increases their surface area, which in turn amplifies their effect. Additionally, the nanosize of the particles enhances their ability to penetrate, which helps to improve the use of the metal properties. Nanoparticles can enter the circulatory system and move even the blood-brain barrier based just on their size obstacle within the human system.

Although their anti-inflammatory properties are also thought to be very helpful in the medical area, silver nanoparticles' antibacterial properties are the ones that are most frequently used in this discipline. According to preliminary research, the decrease in local matrix metalloproteinase (MMP) activity and the rise in neutrophil death within the wound are the causes of the accelerated wound healing observed in the presence of nanoparticles. It has been proposed that MMP may create inflammation, which would prevent wounds from healing [32]. When silver nanoparticles were added to a mouse model of burn injury, it was also shown that the levels of pro-inflammatory cytokines decreased. Additionally, it was discovered that silver nanoparticles can suppress the inflammatory processes of tumour necrosis factor alpha and interferon gamma. Despite the fact that these studies

demonstrate the involvement of silver nanoparticles in the anti-inflammatory effects, the specific mechanism of action is yet unknown. However, because of its anti-inflammatory properties, nanosilver is a great option for usage as an anti-inflammatory drug in a variety of therapeutic applications [33,34]. Artificial joint replacements use bone cements that contain silver nanoparticles. Nanosilver-loaded polymethyl methacrylate is being investigated as bone cement because it contains nanosilver, which has antibacterial properties [35]. The most popular material for creating inserts for complete joint replacement components is ultrahigh molecular weight polyethylene; nevertheless, this material has a significant disadvantage in that it is prone to wear and strain. Silver nanoparticles were added to get around this, and their presence significantly decreased the polymer's wear and tear [36]. Currently, antiseptics and antibiotics are utilised to avoid surgical infections.

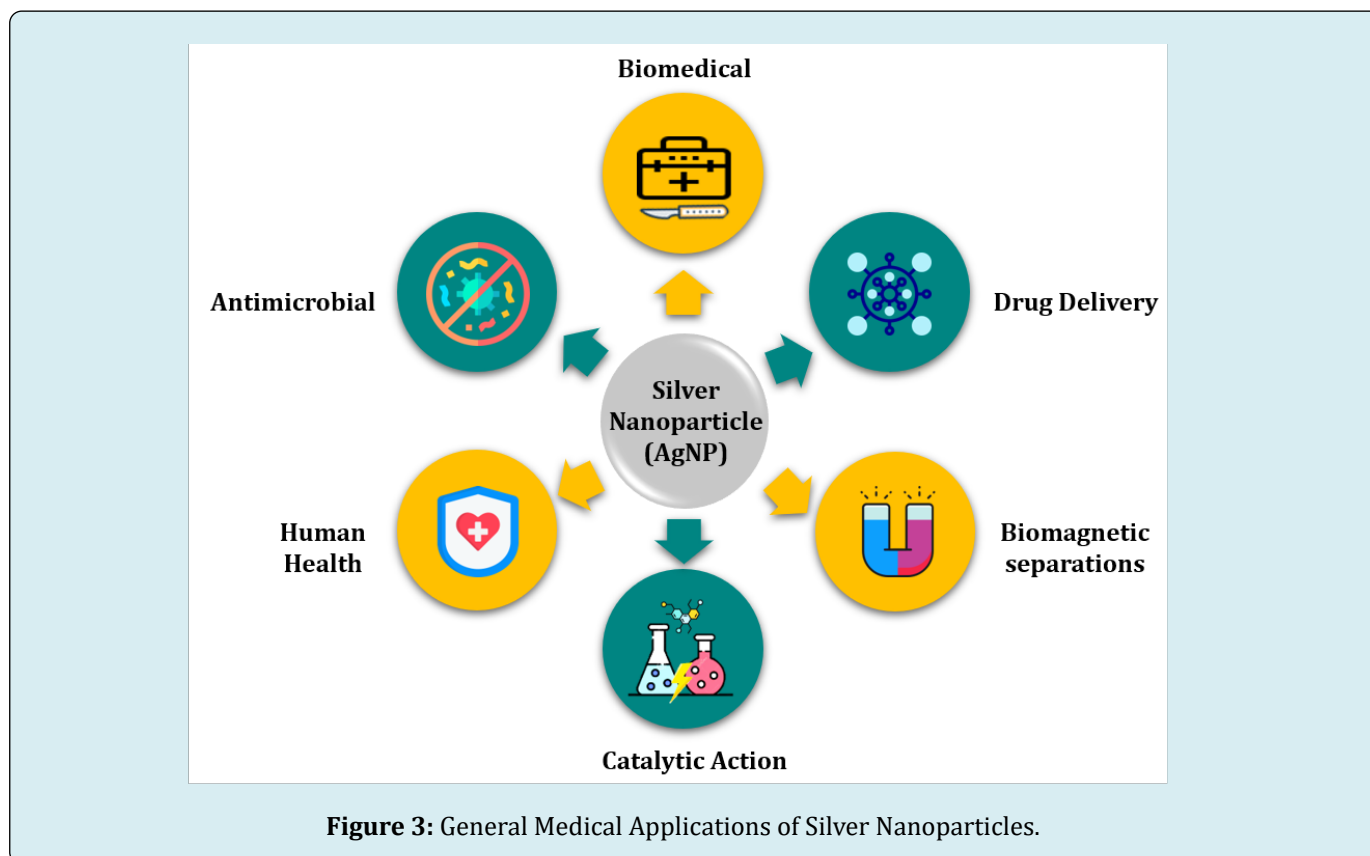
Surgical meshes are utilised for tissue restoration and to bridge big wounds. Despite their effectiveness, these meshes are vulnerable to microbial diseases. Biosensing is another application for nanosilver. The size, shape, and surrounding dielectric medium of nanosilver determine its plasmonic characteristics. It is a prime option for biosensing due to its exploitable dielectric medium features. Many proteins that are difficult for conventional biosensors to detect can be efficiently biosensitized by nanosilver biosensors. Nanosilver's special benefit can be used to identify a number of anomalies and illnesses in the human body, including cancer [37].

Nanosilver's plasmonic characteristics prevent photobleaching, unlike widely used fluorescent dyes, they are also a great option for bioimaging and can be applied

to long-term monitoring of dynamic occurrences [38]. Nanosilver's plasmonic properties can also be utilised to eliminate undesirable cells. After conjugating with the target cells, the cells can absorb light and transform it into thermal energy, which can cause the target cells to thermally ablate [39].

Research conducted over the years has demonstrated that removing silver from the body entirely is challenging. Research on humans and animals has shown that nanosilver

can mostly be eliminated by the faeces, urine, and hair [40]. Biliary excretion, however, is the primary excretion source. Silver particles enter the bile after being taken orally, travel through the liver, and are eventually eliminated through faeces. When inhaled, the particles travel through the lungs, then the bloodstream and other organs before being expelled as urine or faeces. The silver particles can also enter the body through the skin, where they enter the bloodstream, travel to different organs, and eventually be expelled as faeces or urine.



Conclusion

Due to its exceptional antibacterial properties, silver has been utilised for centuries. The distinct chemical and physical characteristics of silver nanoparticles only boost silver's effectiveness. Although the antibacterial activity of silver nanoparticles has been attributed to a variety of processes, the most accurate mechanism is either unclear or cannot be generalised because the nanoparticles have been proven to function differently on various species. Over the years, chemical and physical techniques of creating silver nanoparticles have been used, but they are discovered to be costly and need a variety of hazardous chemicals, which makes biological synthesis the better choice. Although silver nanoparticles have many different applications, their antibacterial and anti-inflammatory properties are the most sought-after and utilised. This has been applied to a number of procedures in

the medical industry and has so been effectively used. Silver nanoparticles' drawback is that they can cause toxicity to varying degrees. Higher concentrations of silver nanoparticles may be harmful and lead to a number of health issues. Studies have also shown that if silver nanoparticles are discharged into the environment, they can cause a number of ecological issues and disrupt the ecosystem. Therefore, it is important to use this wonder wisely and effectively while being aware of its limitations with great caution to ensure that neither the environment nor any person are harmed. It is thought that silver nanoparticles can be a useful ally when handled appropriately, but they can also be a formidable enemy if used carelessly. Therefore, this review ends with the hope and prayer that methods will be developed to eliminate any toxicity that nanosilver may cause to both humans and the environment, allowing for the tremendous use of this substance's special qualities for human benefit without any issues.

Conflicts of Interest

The authors declare that there is no known competing personal relationship or financial interest that could affect the work reported in this paper.

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