REVIEW ON ANTIMICROBIAL, CYTOTOXIC AND GENOTOXIC POTENTILE OF BIOMEDIATED SILVER NANAOPARTICALS

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ABSTRACT

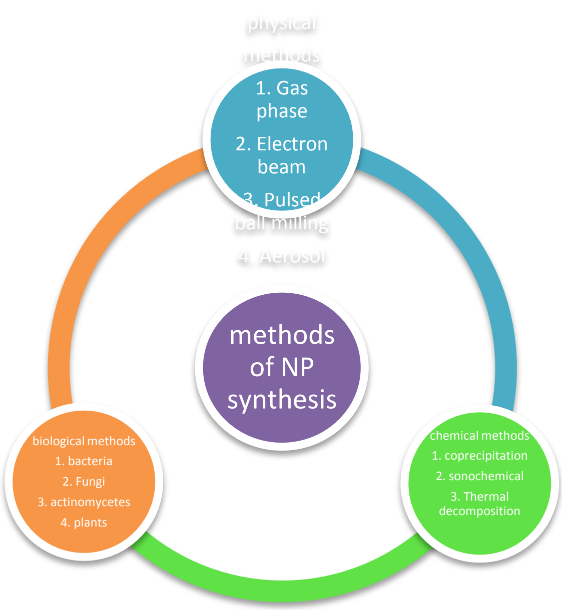
Nanotechnology has changed every industry because of its unique and obvious effects, which have helped scientists make many advances in the medical, agricultural, and other fields. Because they kill bacteria so well, The utilisation of AgNPs is observed in many commercial, household, and Pharmaceutical goods. Since the beginning of human society, silver and silver compounds have been used, Nevertheless, the production of Ag NPs has only lately been made public. In both horticulture and health, they have been used especially as antimicrobials, antifungals, and vitamins. The fact that multidrug-resistant microbes cannot be successfully managed by existing treatments makes them a pressing global concern. Consequently, it is imperative to new antibacterial drugs. Silver nanoparticles (Ag-NPs) are a potential solution of antibacterial substances. It has been demonstrated that by combining Ag/Ag+ with the proteins already present in the microbe cells, Ag NPs prevent many bacteria and fungi from developing and reproducing. Ag NPs have the potential to produce free radicals and reactive oxygen species, which, by obstructing cell reproduction, promote apoptosis and cell death. The SEM as well as TEM photographs of the mixture comprising of pathogens and nanoparticles indicate that the tiny size of Ag-NPs in comparison to microbes enables them to infiltrate cells and result in damage to the cell wall. A lot of research has been done on how metal nanoparticles are made by actinomycetes and how they kill bacteria. Not much attention has been paid to making metal nanoparticles from secondary compounds and new molecules made by actinomycetes. The main focus of the current research is the biosynthesis of metal nanoparticles as well as the possibility of studying compounds made by microorganisms. This study also talks about how to make biogenic metal nanoparticles, keep them from being toxic, and use their unique interactions with biological systems to make them more effective as therapeutic agents in the pharmaceutical and medical industries.

INTRODUCTION

Nanotechnology is the manipulation of structures, devices, and systems at the nanometer scale, which is between 1 and 100 nm (10-9 m) [1].The etymology of the "nano" can be traced back to the Greek term "nano," which denotes "very small" and is the origin of the term "nanometer" [2]. Due to their diminutive dimensions, they exhibit heightened reactivity in comparison to their larger counterparts, possess substantial surface areas, and offer a range of customizable properties [3]. Metallic-NPs have grown in significance in the area of nanomaterials as a result of their distinctive innate features, which are mainly dependent on their form, size, and dispersion. (4). Because of their unique properties, silver nanoparticles are utilised in a diverse array of consumer products, such as textiles, cosmetics, contraceptives, sporting goods, food, packaging, life science and biotechnology applications [5].Ag NPs have exhibited effective bactericidal properties against diverse microorganisms [6]. Microbial-mediated reduction of metal ions is a crucial aspect of bioremediation strategies targeting toxic metals, given the microbial entities' status as nanofactories. (7). The efficacy of several metal salts and metal nanoparticles in has suppressing the proliferation of diverse pathogenic bacteria been uncovered. Ag and Ag NPs hold a versatile position among the metals that have been utilised as antimicrobial agents for several years [8]. The emergence of multidrug-resistant (MDR) bacteria has prompted an urgent need to discover novel antimicrobial agents. As per a scholarly report, silver has been employed as an antimicrobial agent for an extensive duration. The process of synthesising AgNPs through marine actinobacteria holds great curiosity for investigating the capabilities of bacterial extracts as agents for elimination and stabilisation. . The production of AgNPs outside the cell has been documented in various genera such as Actinomycetes, Rhodococcus, Thermomonospora, and Nocardiopsis. [9]. Actinomycetes are considered a promising candidate for large-scale production due to their ease of cultivation and capacity to release a diverse range of extracellular and intracellular biomolecules. Several authors have posited that the cytotoxicity of AgNP is notably impacted by the generation of reactive oxygen species (ROS). (10). Silver nanoparticles (Ag-NPs), which are a form of metallic nanoparticles, possess numerous applications in the advancement of innovative antimicrobial and anticancer agents. (11). Currently, there is a dearth of research pertaining to the genotoxicity and cell-cell interactions of engineered nanoparticles that have been produced at low nanometer scales. There have been few research on the genotoxicity of Ag-NP, particularly in terms of its in vivo impact. Furthermore, the present results of studies on the genotoxicity of AgNPs are inconclusive due to several factors. The toxicity of nanoparticles is influenced by factors such as their size, concentration, and surface functionalization. Park et al. (12) have reported that the amount of Ag-NPs is a crucial factor in determining their cytotoxic, inflammatory, and genotoxic effects. As per the findings of the SOS chromotest, substances such as nanosized Au, Ag, ZnO, and TiO2 NPs, as well as ions of Au, Ag, and Zn, have been classified as non-genotoxic. (13). It can be inferred that biogenic AgNPs generated by marine actinobacteria have potential for diverse biological applications. The study conducted by M. Skadanowski et al. (14) revealed that the biogenic synthesis of silver nanoparticles (AgNPs) using the Streptomyces sp. NH28 strain did not exhibit any adverse effects on the mouse fibroblast cell line. Furthermore, the study found that the AgNPs did not activate NF-B cells at concentrations lower than 10 g/mL.

Characterization and production of silver nanoparticles

The development of nanomaterials can be achieved through three discrete methods, namely physical, chemical, and biological approaches. Figure 1.



2.1. **Physical Method**

The phrase "physical process" encompasses a range of methodologies [15]. Nanomaterials are produced through laser ablation synthesis, wherein a powerful laser beam is directed towards the target substance [16]. As a result of the utilisation of laser irradiation with high intensity in the process of laser ablation, the precursor or original material undergoes vaporization, leading to the formation of nanoparticles. Numerous types of nanomaterials, including oxide compounds, metal nanoparticles, ceramics, and carbon nanomaterials, can be produced using this method [17]. The utilisation of a concentrated beam of light in lithography renders it a valuable method for the creation of nanoarchitectures. Nanoparticles of Carbon underwent ball milling are a distinctive category of nanomaterials that exhibit potential applications in the fields of ecological remediation, storage of energy, and energy conversion, as per previous research [18]. Electrospinning is a fundamental technique utilised for the production of nanostructured materials. Polymers are the preferred choice for the production of nanofibers, owing to their diverse range of constituent elements. The process of sputter deposition involves the physical ejection of small clusters of atoms through the bombardment of a target surface with extremely energetic gaseous ions. [19].

2.2. The Chemical Method

A variety of techniques, including coprecipitation, microemulsion, hydrothermal, electrochemical deposition, and sonochemical methods, have been employed in this field[19,20]. The utilisation of chemical vapour deposition methodologies is of utmost importance in the production of nanoparticles wherein carbon serves as the primary constituent. Precursors that possess desirable attributes such as acceptable evaporation rates, high chemical purity, stable vaporization, low cost, and absence of hazards are deemed ideal for chemical vapour deposition. Moreover, it is imperative that no residual contaminants remain subsequent to its decomposition, as stated in reference [21]. The manipulation of surfactant carbon chain length or the incorporation of supplementary pore-expanding agents can be employed to modulate the pore diameters of nanoporous materials. [22].

2.3. Biological method

Numerous mechanisms are used in the biological process, including produced by fungi, algae, bacteria, yeast, and actinomycetes[23]. When compared to chemical methods, the creation of nanoparticles through a biogenic enzymatic process is considerably superior [24]. The latter approaches are complex, out-of-date, highly valuable, and ineffective, and they produce dangerous toxic wastes that are bad for both the environment and human health [25]. This assertion holds validity despite their ability to expeditiously generate substantial quantities of nanoparticles possessing precise dimensions and configurations.

2.4. NPs from microbes.

2.4.1. Fabrication of nanoparticles by Fungi.

The fungi have many uses in the fields of bioremediation, enzyme synthesis, nanotechnology, and other fields [26]. Since fungi have several advantages over bacteria in the creation of nanoparticles, they have attracted a lot of attention in the generation of metallic NPs [27]. The metal of preference for NP production and research has historically been silver. The following most significant metal ions used by fungi in the creation of NPs include Au, Se and Zn. Species of fungi have been the subject of additional study on NP biosynthesis [28]. The dimensions and morphology of nanoparticles produced by fungi can range from being comparatively simple to being extremely complex, as in the case of Au-NPs produced by Aspergillus sp. and Fusarium strain [29]. It has been discovered that the harmful fungus Fusarium and Verticillium sp. both produce magnetite NPs. [30]. Fungal-derived nanoparticles have been utilised across various disciplines like engineering, biosensors, horticulture, bioimaging, anticancer drugs, antimicrobials, antibiotics, antivirals, diagnostics, and industry. The most widespread uses of NPs have been found to be in agricultural and medical purposes [31]. The amount of nanoparticles produced by fungus is much higher than that of bacteria. More proteins are secreted by fungi, which increases the production of nanoparticles [32].

2.4.2 Fabrication of nanoparticles by yeast.

The intercellular making of NPs using yeast helpful for huge production and convenient processing. By using aqueous silver nitrate as an inoculant, this group was able to extract the silver-tolerant yeast strain MKY3 [[32]. Ag-NPs are formed under artificially constrained biological circumstances [33]. There exist notable distinctions in dimensions, particle arrangement, uniformity, and properties are caused by the various processes that yeast strains from various genera use to create nanoparticles [34Yeast cells have evolved the capacity to transform the metal ions they consume into complex Molecules that are non-toxic.[35]. The potentialof yeast cells to change ingested ions into complex macromolecular compounds is called tolerance. There are several benefits to the fundamental nutrients and the quick growth of yeast strains. For this reason, intracellular synthesised silver, cadmium sulphide, titanium, selenium, and gold nanoparticles are produced by Candida sp. and Saccharomyces sp.[36].

2.4.3. Fabrication of nanoparticles by bacteria.

The majority of the research has been done on prokaryotes that produce metal nanoparticles [37]. The ubiquitous presence of bacteria in the world, and in their abilities to adjust to adverse situations render them valuable subjects for research. Additionally, it exhibits rapid growth, cost-effectiveness in cultivation, and straightforward maintenance. The growth parameters, namely temperature, oxygenation, and incubation time, can be readily manipulated. Bacterial organisms have the capability to produce inorganic compounds within their cellular structures. Ag nanoparticles are produced through a bioreduction process utilising microorganisms, as described in reference [38]. Ag-NPs were generated extracellularly using Pseudomonas stutzeri, as reported in reference 39. Gram-positive and Gram-negative bacterial strains that have been employed for the extracellular and intracellular production of Ag-NPs. They are triangular, hexagonal, cuboidal, spherical, and disk-shaped. They have been created using cells and culture supernatant. It has been demonstrated that Rhodopseudomonas capsulata produces Au-NPs of different sizes, with pH controlling the Au-NPs' shape [40]. Se, Ag, pd, Au, Ti, TiO2 and other metal NPs are thought to be produced by bacteria [41].

2.4.4. Fabrication of nanoparticles by actinomycetes.

These actinomycetes are skilled at creating antibiotic secondary metabolites [42]. The research indicates that Actinomycetes play a significant role in the production of metal nanoparticles [43].The impact of Actinomycetes on the synthesis of metal nanoparticles was observed to be noteworthy. Various eukaryotic and prokaryotic organisms have exhibited the ability to perform biogenic production of metal nanoparticles. Actinomycetes, a microorganism that is relatively less familiar, is employed for the synthesis of metal nanoparticles [44]. Actinomycetes are one of the lesser-known microorganisms used for the production of metallic nanoparticles. Actinobacteria create nanoparticles with strong biocidal activity against a variety of illnesses, good polydispersity, and durability[45]. Streptomyces sp., used to produce Copper- NPs, Silver- NPs, Zinc- NPs[46].

2.4.5. Fabrication of nanoparticles by plants.

The effective synthesis of nanoparticles has been carried out using plant components [47].Highly sophisticated and beneficial for human purposes are plants with low costs and high eco-friendliness. The production of Pd-NPs and Pt-NPs using environmentally friendly methods has been documented [48] The use of different kinds of plants and their various parts allowed for the production of other nanoparticles, such as Ag from AgNO3, ZnO from Zn(NO3)2 and $ZnC_4H_6O_4$, Au from Au_2Cl_6. Helices were discovered to be unaltered by Au-NPs' interaction with human serum albumin [49].

3.Applications of Synthesis NPs

3.1. Water treatment.

Even in its ionic state, nanotechnology has created countless opportunities for water purification [50]. Many nanostructured materials have been developed, and they have characteristics like high aspect ratio, hydrophilic, and hydrophobic interactions that are helpful in adsorption catalysis [51]. Environmental remediation has frequently used nanoscale metals and their oxides, such as Ag,Ti, Au and Fe [52]. Ag-NPs successfully disinfect biological contaminants like bacteria, viruses, and fungi [53], Fig. 2.

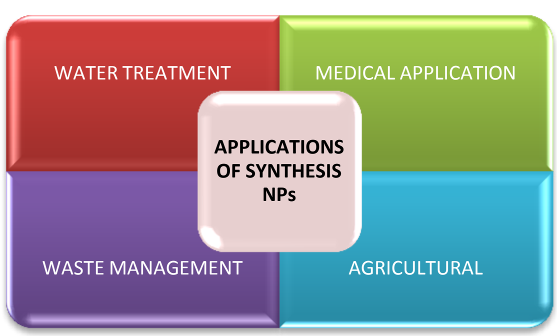


Fig 2: applications of synthesis NPs

3.2. Medical use.

3.2.1. Drug transmission.

As drug transmission methods, nanoparticles can improve the solubility, in vivo stability, pharmacokinetics, biodistribution, and proificiency of free drugs [54]. A wide range of nanostructures have been created for the delivery of medications. Examples of nanostructures or nanocarriers for drug transport include lipid, , Ag-NPs, silica NPs, and drug nanocrystals [55]. Using SPIO-NPs assisted drug delivery devices, pharmaceuticals such as peptides, DNA molecules, chemotherapeutics, radioactives, and hyperthermic agents have all been delivered [56]. Numerous investigations have employed IO-NPs as nanocarriers for the delivery of drugs and genes. By inserting the drug in the necessary location and dosage, nanoparticles can be used to transport the medication to the desired cells. Drug side effects and overall drug consumption are both substantially decreased . One such instance is the development of carbon nanotube structures in bones [57].

3.2.2. Antimicrobial.

Antimicrobial drug resistance in pathogenic bacteria has recently emerged, presenting a significant challenge to the healthcare industry [58]. The development of intelligent surfaces that lower transmission rates is now possible thanks to advances in biological sciences and nanotechnology.The nanotechnology-based solutions described here can help produce materials that limit the generation of airborne viral droplets. when used in biomedical devices and protective gear for medical workers [59]. Research has indicated that metal ions and compounds containing metals efficient antibacterial coatings [60]. The potential antibacterial mechanisms of metal-oxide nanoparticles remain to be thoroughly characterised. Ion densities, oxidative stress, reactive oxygen species (ROS), and membrane disruption have all been identified as potential modes of action against microbes. [61].

3.3. Waste management.

Water is an essential constituent among various components that are indispensable for the sustenance and progression of living organisms. Around 120 crore people lack access to safe potable water, and 260 crore people battle to satisfy their fundamental hygienic requirements. Millions of people, mostly children, have died from illnesses brought on by polluted and contaminated water. [62]. Nanomaterials that could be used in wastewater treatment include polymeric-NPs, metal oxide-NPs, metal-NPs. Yang et al. evaluated chromium Cr(VI) biosorption from synthetic effluent using algal-bacterial sludge. [63]. Nanometals and related oxides, such as TiO_2, ZnO, and CdO are frequently used to eliminate heavy metals, dyes, and ions from wastewater.

3.4. Agriculture.

The ability of nanotechnology to precisely control and release fertilisers, herbicides, and insecticides is causing it to become more popular in agriculture [64]. Goswami et al. discovered that different synthetic NPs, including TiO_2-NPs, SiO_2-NPs, and ZnO-NPs, can inhibit Sitophilus oryzae and B. mori virus infections in silkworms [65]. High sensitivity, low detection limits, excellent selectivity, rapid responses, and small dimensions are all characteristics of nanosensors used to identify pesticide residue. They can also establish the amount of moisture and nutrients in the earth [66].

Table 1. Biomedical application of synthesized nanoparticles from microorganisms

Micro organism	Type of NP	BIOACTIVITY	REFERENCE
Acinetobacter calcoaceticus	silver	Anti bacterial	[67]
Bordetella sp	silver	Anti bacterial	[68]
Gluconobacter roseus	silver	antiplatelet	[69]
Pseudomonas aeruginosa	silver	Bioreducing agent	[70]
Rhodopseudomonas palustris	silver	Anti microial	[71]
Stenotrophomonas maltophilia.	silver	Antimicrobial and cytotoxic activity	[72]
Bacillus licheniformis Dahb1	silver	Probiotic, antibiofilm	[73]
Bacillus subtilis MTCC 3053	silver	Antifugal activity	[74]
Bacillus thuringiensis	silver	Against dengue vector	[75]
Fusarium acuminatum	silver	Anti fungal	[76]
Humicola sp	silver	cytotoicity	[77]

Macrophomina phaseolina	silver	antimicrobial	[78]
Phoma glomerata	silver	antimicrobial	[79]
Pleurotus ostreatus	silver	Inhibitory activity against pathogenic bacteria	[80]
Rhodococcus sp.	gold	Antimicrobial,catalysis and synthesis	[81]
Rhodococcus sp.	Silver	catalysis, biological labelling	[82]
Streptomyces sp.	Zinc	Antibacterial nanopackaging	[83]
Streptomyces sp. NK52 10	Gold	Antilipid peroxidation activity	[84]
Nocardiopsis sp. MBRC-1	Silver	Antifungal and activity against HeLa.	[85]
Streptomyces sp. VITSTK7	Silver	Anti-fungal activity	[86]
Gordonia amicalis HS-11	Silver, gold	Free radical scavenging activity	[87]
Streptomyces sp. VITBT7	Silver	Antifungal and antibacterial activity	[88]
Streptomyces sp. VITPK1	Silver	Anticandidal activity	[89]

4. Cytotoxicity and genotoxicity potential of Ag-NPs

The size, form, coating or capping agent, and type of pathogens used to test the toxicity of nanomaterials all affect how poisonous they are to cells. Nanoparticles produced using green methods are typically more poisonous than those produced using non-green methods. Some organisms are more susceptible to the effects of nanoparticles, specifically Ag NPs, compared to others. This is due to the fact that the released Ag ions as well as the Ag NPs exist. [90]. ROS, which lead to a reduce in glutathione levels and a rise in ROS levels, are thought to be the cause of the cytotoxicity caused by Ag NPs. Additionally, the sample's stability and age play a crucial role because aged Ag NPs that were kept in water for six months have been shown to be more toxic due to the emission of Agions [91]. It appears that the toxicity is a result of the interaction between silver ions and Ag Nanoparticles. Researchers have demonstrated that emitted Ag ions are what causes Ag NPs to be toxic [92]. Ag NPs made from C. thwaitesii leaf extract have demonstrated antibacterial efficacy against *Klebsiella pneumoniae, Shigella fexneri, and Salmonella typhi*, suggesting that they are important. Ag NPs with a spherical shape and a size range of 16 to 38 nm showed good inhibitory efficacy against butyl and acetyl cholinesterase. The HCT-15 was discovered to be toxic to Ag NPs made from L. reticulate. The study found that Ag NPs from an aqueous extract of C. collinus exhibit dose-related impacts on A-549 and normal cell according to Kanipandian et al. [93]. (HBL-100). Although the Ag NPs made from C. collinus were harmful to healthy cells, the IC50 for carcinoma cells was extremely low (30 g/ mL), preventing their use in vivo. Tiny (10–20 nanometer) nanoparticles are more harmful to cells than bigger ones(110 nm), according to Wang et al. [94], and animals with citrate-coated 20 nm Ag NPs had more acute neutrophilic inflamation in their lungs than those with larger ones. ROS production may explain DNA damage and cell viability [95], which may run counter to other researchers' results from in vitro studies. Ag NP interactions with repair mechanisms are thought to be the cause of irreversible DNA damage. Since this research was conducted in vitro, it's possible that broken DNA won't be able to be repaired. Nanoparticles adhere to bacterium cell walls because they are tiny than the cells, it inhibits the absorption of vital nutrients and kills microorganisms. [96]. Besides their applications in various fields, Ag NPs are widely used as antioxidants and antibacterial agents, regardless of their synthesis process [97, 98]. Smaller particles have more surface area because of their smaller size, and when they aggregate around a microbe's cell wall, they prevent the reproduction of its cells. Regardless of the method of synthesis, Ag NPs are widely used as antioxidant and antimicrobial compounds in a variety of applications [99]. Allahverdiyev et al. [100] noted that combining Ag NPs with antibiotics reduces the required dose and reduces toxicity to human cells**.** For microbes, they are more toxic than for people. Ag NPs were tested for their antibacterial and antifungal properties against the bacterium B. cereus, S. aureus, C. koseri, P. aeruginosa, and the fungus C. albicans, respectively. According to one theory, once inside the bacterial cell, Ag NPs engage with the thiol, hydroxyl, and carboxyl groups, deactivating the essential processes by releasing $Ag+$ ions. In order to protect microorganisms from exposure to these kinds of nanoparticles on a regular basis, precautions should be made. Additionally, HeLa , MDA-MB-231, A549 , and HEP2 have all demonstrated that treatment with bacterial Ag NPs reduces cell viability in a dose-dependent way. Ag NPs made from bacterium strains showed cytotoxicity to cancer cells, but their effects on healthy cells must also be taken into consideration. Numerous writers have claimed that cytotoxicity is significantly influenced by the production of reactive oxygen species by AgNP (99). In vivo experiments have demonstrated that exposure to Ag-NP induced oxidative stress and elevated levels of reactive oxygen species (ROS) in the sera of rats subjected to the exposure. (100). Numerous academic studies have demonstrated that Ag NPs induce biological and genetic changes that are linked to genetic damage such as DNA breaks. Genotoxicity is characterized by mutations ranging from types of DNA damage and genetic to structural chromosomal alterations increase(101). Limited research has been conducted on the genotoxicity and biological interactions of nanoparticles that are manufactured at a reduced nanoscale dimension. Limited research has been conducted on the potential genotoxic impacts of Ag NPs, particularly in relation to their effects on organisms that are alive. The variability in outcomes of studies investigating the genotoxicity of AgNPs can be attributed to several factors. Ag-NP size is a significant determinant for cytotoxicity, inflammation, and genotoxicity, according to Park et al. (12). Due to TiO2 NPs' exceedingly low solubility, the genotoxicity of the Ti ion was not examined. IFmax values of less than 1.5 for all chemicals show that Au NPs, Ag NPs, ZnO NPs, TiO2 NPs, and ions of Au, Ag, and Zn, in a variety of tested concentrations, had no impact on the SOS chromotest. According to M. Skadanowski et al. (14), the NH28 strain did not interact negatively with the mouse fibroblast cell line and did not cause any NF-B cells to become activated at concentrations below 10 µg/mL.

5. Conclusions

Differently shaped nanoparticles are a common form of nanomaterial that has contributed Regarding the progress of nanotechnology.Researchers who are interested in these methods have recently created their own nanocomposites as a result of recent advancements in the properties of novel nanomaterials and their uses. In the globe, Silver nanoparticles are extensively utilised nanomaterials. Ag-NPs are widely used in a variety of consumer products and applications for the life sciences and biotechnology, thanks to their potent antibacterial properties. Numerous illnesses, such as cancer, lupus, typhoid, TB, and malaria have all been treated with them (FDA, 1999). Although Ag NPs have the potential to enhance ecological and human well-being, their interactions with nature are inescapable, and the extent of their impact on human health and ecosystems remains incompletely comprehended. Furthermore, there is an increasing apprehension regarding the adverse effects of Ag-NPs on human health and the ecosystem. Silver nanoparticles (Ag NPs) offer several advantages, however, they also possess certain limitations. It has been noted that Ag NPs are efficient against microbes. Ag NPs are expected to be used as a low-cost, broad-spectrum antimicrobial, cytotoxic, and safe genotoxic agent to safeguard plant harvests and treat infections in humans.

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