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THERAPEUTIC APPLICATIONS AND MECHANISM OF ACTION OF PLANT-MEDIATED SILVER NANOPARTICLES

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Abstract

Nanobiotechnology plays an important part in today's medical diagnosis and treatment. Nanoparticles which can be biosynthesized have characteristics such as biological compatibility the cost-effectiveness and friendly to the environment, resulting in potential candidates for various biomedical and biotechnology applications. The significance of silver nanoparticles is in their unique physiochemical, antimicrobial, and anticancer characteristics, as well as their wide variety of applications in fields such as wound care management, pharmaceuticals, electronics, biomedicine, textiles, cosmetics, therapeutics, photonics, and agriculture. Silver nanoparticles (Ag NPs) can be synthesized through various methods including chemical, physical, and biological techniques. Biogenic silver nanoparticle precursors with distinct geometry and surface qualities can be synthesized by plants, bacteria, and fungi. This review explored the properties of biogenic Ag NPs and their potential as agents with anticancer, antibacterial, and antifungal properties.

Key words: Silver nanoparticles; Antimicrobial; Anticancer; Green synthesis; Plant extracts.

Introduction

Sustainable nanotechnology is successful in science and engineering in offering solutions for problems in a wide range of geographical regions, including the agricultural sector, catalysis, industries, and pharmaceuticals (Beyene *et al*., 2017; Mata *et al*., 2012). Nanotechnology is a fast-expanding field, which produces innovations in consumer goods, nano-electronics, environmental cleanup, healthcare, and aerospace engineering (Singh *et al*., 2009). Nnaoparticles are bacically material with atleast having one dimension below 100 nm and their size ranges from 10-100 nm (Hussain *et al*., 2016; Rahman *et al*., 2019). According to consensus, nanoparticles are atom clusters between one and one hundred nanometers in size (Williams, 2008).

Standard physical and chemical nanoparticle production techniques are rarely used because of their toxic nature, demanding energy consumption and cost processing steps after manufacture. Unlike conventional approaches, biological silver nanoparticle synthesis is efficient, produces higher, and requires a cheap method of preparation. Thus, many biological processes which include microorganisms to synthesize nanoparticles were readily available (Konishi *et al*., 2007) and plants or plants extracts eco-friendly approaches to both physical and chemical processes (Das *et al*., 2013; Shah *et al*., 2021; Qasim *et al*., 2019; Nasar *et al*., 2019).

Numerous sizes, shapes, and types of metallic nanoparticles exist, such as those made of cerium, titanium, platinum, thallium, iron, gold, and silver (Elizabeth *et al*., 2019). There are two ways to make metal nanoparticles. The first is a physical strategy that makes use of several techniques like evaporation or condensation and laser ablation. The other method is the chemical method, and it involves reducing the metal ions in solution under circumstances that will eventually lead to the production of tiny metal clusters or aggregates (Oliveira *et al*., 2005). Several *In vitro* and *In vivo* studies have been conducted on Ag NPs over time to determine how hazardous they are to biological tissues and organisms (Marin *et al.,* 2015). They can be used in textiles, food production, household, and personal care products, medical devices, and personal care products, as well as personal care and household products (de Lima *et al*., 2012; Durán *et al*., 2010). Nanoparticles such as silver, gold, zinc, cadmium sulfide, copper, iron, titanium dioxide, as well as others exhibit unique characteristics (Akter & Huq, 2020; Huq *et al*., 2022).

Silver nanoparticles (Ag NPs) have a vast range of flexible properties that support their use in a variety of biomedical and related applications. Silver nanoparticles, also referred to as Ag NPs, are currently used extensively in many different areas such as preservation of food, the medical field, textile coatings, and applications in the environment. The efficacy of their use as antibacterial, anticancer, and antifungal agents has been well-supported (Abou El-Nour *et al*., 2010). Silver nanoparticles are commonly used nanomaterials because of their wide-ranging antimicrobial properties, flexibility, and becoming more prevalent a commercial availability. Silver nanoparticles (Ag NPs) are currently being studied for their potential to function as anticancer agents. There is growing, evidence that silver nanoparticles made through mycosynthesis have broad-spectrum antibacterial efficacy against bacterial strains that are resistant to multiple drugs (Singh *et al.,* 2014). This review aims to provide a comprehensive overview of the synthesis method, parameters, different characterizations, as well as applications of silver nanoparticles. More specifically, the focus will be on thoroughly investigating the antibacterial, anticancer, and antifungal mechanisms. The main objective of this review is to contribute to the development of more efficient antimicrobial compounds and encourage further study into novel cancer treatments, microbial disease transmission, and other biological applications.

Table 1. Examples of plant-mediated green synthesized silver nanoparticles and their biological activities.

Plants and microorganisms used	Bioactivity	Type of used extracts	Disease-causing pathogens	Effective concentration	References
Dunaliella salina	Anticancer	Aqueous extract	Cell line (MCF-7)	25,50 µg/mL	(Singh *et al.*, 2017)
Bauhinia tomentosa	Anticancer	Leaf extract	Cell line of lung A-549	28.125 µg /Ml	(Mukundan *et al.*, 2015)
Nepeta deflersiana	Anticancer	Aqueous extract	Human Cervical Cancer Cell	2,5 µg /mL	(Al-Sheddi *et al.*, 2018)
Cynara scolymus	Anticancer	Leaf extract	MCF7 cell	10 µg/mL	(Erdogan *et al.*, 2019)
Ginkgo biloba	Antifungal	Fruit extract	*Bipolaria maydis*	200 µg/mL	(Huang *et al.*, 2018)
Acalypha indica	Antifungal	Leaf extract	*Alternaria alternate, Sclerotinia sclerotiotrum*	15 mg	(Krishnaraj *et al.*, 2012)
Candida albicans	Antifungal	Mycelium extract	*Trichophyton rubrum; T. mentagrophytes* and *Microsporium canis*	4 µg/mL	(Guilger-Casagrande & Lima, 2019)
Oryza sativa L.	Antifungal	Leaf extract	*Magnaporthe grisea*	10-30 µg /mL	(Elamawi & El-Shafey, 2013)
Plantago major L.	Antibatcerial	Leaf extract	*E. coli*	20 µg/mL	(Huq *et al.*, 2022; Sukweenadhi *et al.*, 2021)
Taraxacum officinale	Antibacterial	Leaf extract	*Xanthomonas axonopodis, Pseudomonas syringae*	20 µg/mL	(Saratale *et al.*, 2018)
Moringa oleifera	Antibacterial	Leaf extract	*Proteus vulgaris*	30 µg/disc	(Islam *et al.*, 2021)
Ricinus communis	Antibacterial	Leaf and root extract	*S. pneumoniae, E. coli, S. aureus*	20 µg/mL	(Gul *et al.*, 2021)
Terminalia catappa	Antibacterial	Leaf extract	*Candida albicans*	7.8 µg/mL	(Ansari *et al.*, 2021)
Lampranthus coccineus & *Malephora lutea*	Antiviral	Aqueous extract	*VERO cells, CoxB4*	5.28 µg/mL	(Haggag *et al.*, 2019)
Fusarium oxysporum	Antiviral	Filtrate of biomass	*Herpes Simplex* Virus & Human *Para influenza* Virus Type3	100 µg/mL	(Gaikwad *et al.*, 2013)
Sargassum wightii	Antiviral	Filtrate of dried powder	HSV-1 & HSV-2	ID_{50} 2.5 µL	(Dhanasezhian *et al.*, 2019)
Panax ginseng	Antiviral	Root extract	*Influenza A virus*	0.02 & 0.25 M	(Sreekanth *et al.*, 2018)
Moringa oleifera	Antiviral	Seed extract	*Dengue virus* (DEN -2)	20 µl/ mL	(Jain *et al.*, 2021)

Green synthesis of silver nanoparticlesaterial: Many researchers have performed studies on the ability of plants to synthesize nanoparticles with different dimensions and shapes, and their significance across many biological applications. The scientific investigation of biosynthetic pathway compounds from a physiological point of view seems to be overlooked. Investigating the mechanisms and pathways that result in the cutting or forming of large quantities of material into nanoparticles becomes essential for developing a methodology to produce nanomaterials with the appropriate size and morphological characteristics. The production of nanoparticles involves three different phases, including the nucleation process growth and development, and capping (Javed & Mashwani, 2020). The exact mechanism of primary or secondary metabolites that regulate the activation of metallic salts into nanoparticles is still undefined. Yet, they significantly influence throughout the bulk material, which results in the formation of the nuclei with consistent sizes and shapes (Sadalage *et al.*, 2020). Plant pathogens and their infections cause 30 % losses in staple crop production worldwide (Fadiji *et al.*, 2022; Savary *et al.*, 2019). Traditional plant disease treatment relies heavily on chemicals that harm humans and the environment. Many modern pest management fields are environmentally friendly. Biocontrol agents and endophytic microbe-derived NPs are examples. The size, shape, and stability of nanoparticles can be strongly affected by many factors such as the pH, temperature, medium in which they grow, synthesis condition, and surface condition (Ovais *et al.*, 2018). This study reveals how silver nanoparticles can suppress microbial plant diseases.

Many research investigations have been carried out on the biosynthesis of Ag NPs including fungal organisms; however, its exact processes remain poorly elucidated. It has been suggested that the process of synthesizing nanoparticles without entering a cell occurs via enzymatic reactions present in the fungal filtrate, which serve to reduce Ag ions and produce elemental Ag at the nanoscale and level of responsibility. The absorbance wavelength of the bands comes in within the range of 350-500 nm. A higher wavelength peak of absorbance shows the presence of larger nanoparticles (Elamawi & El-Shafey, 2013). The size hinges on the combination of conditions such as fungus species, pH, temperature, dissipation medium, also the presence of capping on the nanoparticles (Khandel & Shahi, 2018). It was previously found that the synthesis process occurs through the action of the compound NADPH without requiring a presence of the nitrate reductase enzyme (Hietzschold *et al.*, 2019).

The use of plant-mediated silver nanoparticle production is becoming increasingly popular due to their effectiveness and the availability of plants. Many different parts of plants such as roots, fruits, flowers, and leaves, as well as protective coverings have been used in the process of green synthesis of biologically active silver nanoparticles. The extracts of plants that were used in this process contain a wide variety of bioactive compounds, which include but are not limited to alkaloid compounds, flavonoids, terpenoids, tannins, sugars, phenols, vitamins and minerals, enzymes, amino acids, peptides, and proteins (Singh *et al.*, 2016; Sukweenadhi *et al.*, 2021; Khalil *et al.*, 2020). Many plants can synthesize silver nanoparticles (Table 1). Silver nitrate solution and plant-derived reduction chemicals are used to make green Ag NPs. Following the Au NPs method, plant extracts are coupled with silver nitrate solution. The solution turns brownish when Ag NPs form (Hemmati *et al*., 2019; Rautela & Rani, 2019).

Therapeutic applications and mechanism of action: The field of "green nanotechnology" has experienced a significant increase in interest because of the increasing popularity of nanoparticle biosynthesis. The biological and physical characteristics of nanotechnologies make them useful in pharmaceutical delivery and applications involving biosensors. The research study of green synthesis of nanoparticles as an environmentally friendly method in plant use is an area appropriate for scientific investigation. The application of phyto-nanotechnology has the potential to successfully control and/or mitigate different kinds of cancer. The syntheses of nanoparticles with antibacterial, antioxidant, and anticancer properties can be accomplished through collaboration among various fields of natural science, especially those concentrating on plant-mediated methods. Nanotechnologies have the potential to help with the development of therapeutic products that are both more effective and less hazardous (Dipankar & Murugan, 2012). Environmentally conscious products have increased interest in plant-based nanoparticles. Synthesis of nanoparticles using plants provides many advantages, such as cleaner solvents, lower usage of toxic chemicals, softer response conditions, efficiency, and adaptability in medical, surgical, and pharmaceutical applications (Abdel-Halim *et al*., 2011). Because they can disrupt the mitochondrial respiratory chain, which produces reactive oxygen species (ROS) and ATP production, which can cause DNA damage, Ag NPs function well in cancer treatments (Chung *et al*., 2016). The other mechanism for Ag NPs production involves reducing, chelating, and stabilizing nanoparticles containing secondary metabolite functional groups. Oxidation/ reduction reactions between plant secondary metabolites and silver salt reduce silver ions. Redox reactions generate ions and molecules (Duan *et al*., 2015; Javed & Mashwani, 2020). The plant-based Ag NPs have been investigated for their anticancer, antidiabetic, and antibacterial activities, in addition to their unique synthesis mechanism. Fig. 1 presents a comprehensive summary of the review.

Antibacterial activity of Ag NPs: According to several scientific researchers, the incorporation of silver nanoparticles into water may result in their conversion into silver ions (Ag), which hold the ability to kill pathogens (Liu *et al*., 2009). Numerous researchers point the effective antibacterial role of Ag NPs to the very small and large surface area, membranes of the microbes can be simply destroyed while Ag NPs enter and degraded into silver ions Ag in the cell and destroy the intracellular structure (Pal *et al*., 2007). AgNPs' antibacterial effects had been known for several decades, but scientific evaluation began in the 2000s. Sondi and Salpek-Sondi were the first to show how Ag NPs affected *Escherichia coli* (*E. coli*). Bacterial cell walls formed "pits" and Ag NPs increased plasma membrane permeability, damaging the cells. Ag NPs immediately interact with the bacterial cell membrane, destroying it and cell components (Sondi & Salopek-Sondi, 2004).

Mechanism of antibacterial activity of Ag NPs: The exact cellular mechanism by which Ag NPs exert their impact is still unexplored. A variety of botanical extracts have shown the ability of Ag NPs to become involved in physical interactions with the surfaces of bacterial cells. The impact of Ag NPs on cells can be seen through their interaction with bacterial cell walls and membranes, the way that they invade cells and cause damage to organelles within cells and biological molecules, their potential to trigger oxidative stress in the cells, and their regulation of pathways for signaling (Dakal *et al*., 2016). In microbial cells, the phosphorylation cycle and dephosphorylation pathway relay growth and activity signals. Ag NPs cell-acting mechanism is unknown. Ag NPs can interact with bacterial cell surfaces, according to plant extracts (Mikhailova, 2020; Shrivastava *et al*., 2007). Silver nanoparticles damage cell membranes and disrupt respiratory chain enzymes, causing cell death (Escárcega-González *et al*., 2018). Silver NPs' cytotoxic action comes from their ROS production (AshaRani *et al*., 2009). Scientists believe silver nanoparticles interact with the bacterial cell membrane, although the primary target is unknown (Bondarenko *et al*., 2018). Antibacterial silver nanoparticles tackle 650 illnesses. Several studies have shown that Ag nanoparticles plus antibiotics can kill multidrug-resistant bacteria like *Staphylococcus aureus* and *Escherichia coli* (Elbehiry *et al*., 2019; Surwade *et al*., 2019).

Another finding demonstrated that NPs not only break down and enter the plasma membrane, changing its structure and absorptivity but also pass through the cell, where they may magnetize sulfur or phosphorus groups inside the cell and deform DNA and proteins. The modification of the respiratory system within the membrane can be assisted by the interaction of specific items with thiol groups present in enzymes that possess reactive oxygen species as well as free radicals. This interaction may result in the damage of intercellular machinery and the beginning of the apoptotic pathway. The interaction between silver ions produced by nanoparticles and within biological components has the potential to influence many different biological processes, such as but not limited to the membranes, metabolic processes, and genetic material (Gomaa, 2017). Nanoparticle size and antibacterial action are interrelated. Smaller nanoparticles can easily reach the cytoplasm and interact with microbial cells, their components, and organelles and figure 2 depicts the anticipated mechanism of nanoparticles' influence (Abbaszadegan *et al*., 2015; Mikhailova, 2020).

Antifungal activities of Ag NPs: Immunosuppressed patients have several fungal infections, but very few antifungal agents are available (Rahman *et al*., 2019). Therefore, safe, biocompatible, and eco-friendly antifungal agents should be synthesized immediately. Yeast and mold infections are an increasing healthcare issue as modern therapy prolongs the lives of critically ill patients. These germs infect HIV, cancer, organ transplants, surgery, ICUs, and newborn newborns. Fungi are a type of eukaryotic organism that exhibits greater genetic diversity than bacteria. This characteristic presents a challenge in the accurate diagnosis and treatment of infections caused by fungi, that is responsible for the substantial mortality rates related to these diseases, thereby providing current therapeutic techniques insufficient (Perlroth *et al*., 2007). Silver nanoparticle antifungal activity is less studied than antibacterial activity. The PubMed research on silver nanoparticles' antibacterial efficacy showed 590 articles (up to May 2013), but the number of antifungal studies was only 70 (Kim *et al*., 2008). Nowadays, Ag NPs have achieved a lot of attention because of advances in curing bacterial infections and diseases, also ineffective analysis showed that they are potentially harmful to fungi also (Ahmad *et al*., 2020; Huq *et al*., 2022). Previous study shows that biosynthesized Ag NPs from *Aspergillus nigar* was the utmost aroused fungus that had the greatest zone of inhibition (Qasim Nasar *et al*., 2019).

Rice is considered an important food product for approximately half of the world's population. Rice provides an important position in Egypt as the second most essential staple food, following wheat. It plays an important part in both domestic usage and exports. Rice cultivation is mainly carried out in the Northern region of the Nile Delta in Egypt, spanning over an area of one million feddans annually. In the 2010 agricultural season, a total of 1.77 million feddans were utilized for cultivation, resulting in a yield of 6 million tons of paddy rice. According to the RRTC (2010), the crop in challenging yielded an average of 10.06 tons per hectare, which is one of the leading yields globally. The production of rice exhibits a reduction of 5 % in traditional or low cases of famine. However, in years of epidemic outbreaks, the losses in yield may reach up to 30-50 % (Sehly *et al*., 2002). Fungicides are commonly used for the purpose of combating blast diseases. Still, their effect is limited due to the potential of cultivating resistance (Dashora *et al*., 2022).

Mechanism of antifungal activity of Ag NPs: Different species of pathogenic fungi *Sclerotinia sclerotiorum*, *Curvularia lunata*, *Macrophomina phyaseolina*, *Rhizocotonia solani*, *Botrytis cinerea*, and *Alternaria alternate* used as examining organisms and were grown in PDA medium and where well-diffused analysis was accomplished to find out activity of Ag NPs which were biosynthesized. Silver nanoparticles were used in concentrations and were mounted into each well of PDA plates and inoculated plates were incubated at room temperature, at the end zone of inhibition was checked (Singh *et al*., 2020). Different grew strains of fungus on SDA (Saboured Dextrose Agar) and appended in tween 20 (0.02%) solution and maintained turbidity (0.5) McFarland solution, plated were adapted and besom with 100 µL of yielded spores. Antifungal drugs i.e., amphotericin (as positive control) and DMSO (as negative control) were used, then incubation was done at 28ºC, after that zone of inhibition of growth was checked after 1-2 days by using a Vernier Caliper (Qasim Nasar *et al*., 2019).

Abstracted *R. solani* from defiled sheaths of rice plants, asserted it on PDA at 30ºC for 1 week, maximum growth was obtained, and purification of culture was done by sub-culturing, then inoculation was done by placing agar cork having mycelia placed in the center of PDA plates and incubated at 30ºC. A poison food approach was applied to check the *In vitro* competence of *D. malabarica* combined with ZnO and Ag NPs against *R. solani*. The altered concentration of stock solutions was used by mixing with PDA, then autoclaved media along with some combination of NPs was transferred to petri- plates; half month-old culture was employed in the analysis. ZnO and Ag NPs showed antifungal ability against *R. solani* up to 50% abridgment in growth, while *D. malabarica* boosts Ag NPs manifest highest growth hindrance adjoin to *R. solani* as opposed to ZnO-NPs (Jannat *et al*., 2022). Fig. 3 shows silver nanoparticles predicted antimicrobial activity. Ag NPs produce Ag^+ ions that accumulate on microorganisms' cell membranes and cell walls and penetrate cytoplasm. Ag^+ ions generate reactive oxygen species (ROS) inside the cell, which inhibit DNA synthesis, mRNA synthesis, cell membrane destruction, protein synthesis, cell-wall synthesis, and mitochondrial damage these effects finally lead to cell death. Ag NPs destroy microorganisms and release silver ions.

Anticancer activity of Ag NPs: Cancer, a group of diseases, causes various pathological and metabolic changes in cellular environments. The growth and progression of the condition is made possible by distinct signaling mechanisms, including metastatic disease, angiogenesis, and proliferation of cells (Seigneuric *et al*., 2010; Ovais *et al*., 2017). Mitochondrial DNA depletion, aerobic glycolysis, changes in respiratory chains, and genetic expressions are all abnormal metabolic procedures in cancer cells. At certain stages, the effectiveness of physical and chemical cancer treatments is restricted. However, existing treatments have negative side effects and interfere with usual cell activity while exposing patients to extreme doses of medication and radiation (Wu *et al*., 2011). During the past few years, there has been a little increase in cancer cases, most of which result in death (Raghunandan *et al*., 2011). We must create effective medication delivery systems for a variety of cancer types so they can be used as effective chemotherapeutic medicines (Abdel-Fattah *et al*., 2017).

Recent reports have shown the significant upside potential of Ag NPs as combination partners, as they have been found to regulate Pgp function as well as improve the therapeutic effect of chemotherapy against cancer cells that are resistant to numerous medications (Igaz *et al*., 2016). The most common cancer kind overall, according to reports, is breast cancer (13.7%), which is followed by colorectal cancer (11%). Due to the severely impaired immune systems of these patients, the current chemotherapies for these two most common cancers mostly result in other problems such as infections by bacteria, fungi, and viruses. Numerous cytotoxic medications, including doxorubicin, cisplatin, and bleomycin, are used to treat breast cancer, but they all have disadvantages and are ineffective. The field of nanomedicine focuses on the creation of novel therapeutic and diagnostic tools for use by humans by using nanoparticles that have undergone precise engineering (Tabrez *et al*., 2020). The use of nanoparticles as anticancer nanomedicines to target and treat malignant cells is possible (Oves *et al*., 2018).

Mechanism of anticancer activity of Ag NPs: The production of reactive oxygen species (ROS) induced by plant-based silver nanoparticles (Ag NPs) has been identified as an initiating factor in cellular apoptosis (Fig. 4). ROS effect signal transduction mechanisms cause apoptosis. Mitochondrial transmembrane potential H_2O_2 radicals induce respiration uncoupling (Fani *et al*., 2016; Javed *et al*., 2021; Ullah *et al*., 2020). Additionally, p53 protein upregulation by some researchers believes plant-based Ag NPs trigger cell death and toxicity (Halawani *et al*., 2020). The size and form of Ag NPs affect their cytotoxicity. For instance, it was observed that human lung epithelial A549 cells may be susceptible to cytotoxicity when it is exposed to Ag NPs with dimensions of 100-160 nm, 1.5-25 m, and

30 nm spherical morphologies (Sankar *et al*., 2013). Ag NPs can be dangerous at greater doses but are harmless at lower doses. Normally, cells exposed to different NP concentrations exhibit an increase in cell inhibition that is dose dependent. Different Ag NPs formulations have dosage effects that might change cytotoxicity or enhance anticancer efficacy. Numerous studies have shown that Ag NPs produced through biosynthetic pathways have anticancer properties. However, Ag NPs produced through biosynthesis exhibit some degree of cytotoxicity as well (Kim *et al*., 2014; Priyaragini *et al*., 2013). Additionally, a lot of the NPs created from plant sources had a spherical form and showed significant effectiveness against cancer cell lines.

Angiogenesis refers to the process of producing novel blood vessels from previous ones, which can lead to different consequences such as the development of tissue granulation and healing of wounds. Blood vessels play an important part in the supply of various nutrients and removal of toxic substances at the tissue level (Birbrair *et al*., 2014). According to Folkman's theory, the development of new blood vessels is what causes solid tumors to grow (Bhat & Singh, 2008). The regulation of this process, which involves the influence of both activator and inhibitor molecules, is believed to play an important part in the beginning and growth of cancer. According to this theory, the progression of malignant tumors is reliant upon sufficient blood flow. The formation of new blood vessels promotes tumor growth by providing cancer cells with sufficient oxygen and nutrients to penetrate and spread throughout the body (Folkman, 2002).

Green-synthesized Ag NPs were found to alleviate retinal neovascularization-like disorders (RNV). They suppressed VEGFR-2-induced RNV and ERK1 activation by regulating its phosphorylation. These anti-angiogenesis properties have helped treat cancer with Ag NPs (Shen *et al*., 2015). Several justifications have been discovered by scientists that argue for the anticancer properties of silver nanoparticles. Silver nanoparticles can enter and accumulate within cancer cells due to their higher permeability as well as retention effect (EPR), which eventually leads to the inhibition or damage of cancer cell division. The effect of silver nanoparticles on signaling physiological pathways has been noticed to end up resulting in either early apoptosis or lower tumor cell division. According to other research, silver nanoparticles trigger a series of biological events resulting in apoptosis and cell division by activating p53, caspase-3, and p-Er K1/2 (Gurunathan *et al*., 2015). Miriam Buttacavoli and her colleagues investigated the mechanistic pathway of silver nanoparticles on the SKBR3 breast cancer cell line, using modern tools and processes. The findings of the study provide a conclusive knowledge of the mechanism that supports the anticancer potential of silver nanoparticles on human cancer cell types, specifically SKBR3. The researchers observed a substantial reduction in cellular motility, along with inhibitory impacts on metalloproteinases (MMPs).

The application of silver nanoparticles caused significant modifications in the morphology of cancer cells, such as reduction in size, irregular shape, cytoplasmic blebbing, alteration in the arrangement of intracellular vacuoles, and the condensation of the chromatin structure The study suggests that the EPR phenomenon resulted in the elevated uptake as well as retention of nanosilver by cancer cells, leading to the generation of extremely toxic silver ions (Torchilin, 2011). Oxidative stress degrades key biomolecules, disrupts physiological processes and molecular pathways, destroys essential cellular organelles and biomembranes, and kills tumor cells (Al-Sheddi *et al*., 2018). VEGF creates new blood vessels, which promotes angiogenesis, a significant cancer process (Carmeliet, 2005). Silver nanoparticles inhibit VEGF, making them anti-angiogenic (Kalishwaralal *et al*., 2009). Silver nanomaterials serve as delivery systems for therapeutic anticancer payloads (drugs), increasing their effectiveness and potency while preventing cancer cells from developing resistance to them. Moreover, they encourage the exact management of antineoplastic agents, consequently mitigating the cytotoxic effects of chemotherapy on non-malignant tissues (Karuppaiah *et al*., 2020; Patra *et al*., 2015).

Antiviral activities of Ag NPs: The crucial importance of the development of antiviral drugs results from the widespread use of diseases caused by viral agents, that exhibit an increased prevalence on a worldwide basis. Knowing about the mechanisms that support the antiviral effects of Ag NPs is an important component of the treatment of viruses. Ag NPs exhibit a distinctive mechanism for interaction with bacteria and viruses, reliant upon specific size and shape parameters (Lok *et al*., 2006; Zhang *et al*., 2016). Metals can be investigated for antiviral activity, but little is known about how metal nanoparticles interact with viruses. However, current findings have demonstrated that metal nanoparticles can fight HIV-1, hepatitis B, respiratory syncytial, and herpes simplex viruses (Lara *et al*., 2010; Speshock *et al*., 2010). The most recent research conducted on the human parainfluenza virus type 3 and the herpes simplex virus has shown that biologically synthesized silver nanoparticles (Ag NPs) exhibit the ability to inhibit or minimize viral replication, reliant upon their size and zeta potential (Gaikwad *et al*., 2013; A. S. Jain *et al*., 2021; N. Jain *et al*., 2021).

Mechanism of antiviral activity of Ag NPs: Silver nanoparticles exhibit effective antiviral properties. Silver nanoparticles (Ag NPs) attach to the viral genome, thereby blocking the activity and interaction of viral and cellular components that are responsible for viral replication. The antiviral mechanism of Ag NPs can be seen in Fig. 5. The interaction between viruses and Ag NPs can be boosted by various factors such as size, shape, charging at the surface, dispersity, and protein corona effects (Allawadhi *et al*., 2021; Auría-Soro *et al*., 2019). The gp120 is the target of Ag NPs viricidal activity against HIV-1, and they also prevent gp120 from attaching to host cell membranes. As a result, entrance, fusion, and infectivity are blocked (Lara *et al*., 2010). AgNPs destroy viruses, although the precise method by which they do so is unknown. Silver nanoparticles (Ag NPs) have the potential to be utilized as an antioxidant against different viral infections, including those caused by the herpes simplex virus (HSV), respiratory syncytial virus, and adenovirus type 3 (ADV3). This can be done by blocking the spread of viral infection in cells or by direct deactivation of the viruses (Morris *et al*., 2019; Ratan *et al*., 2021).

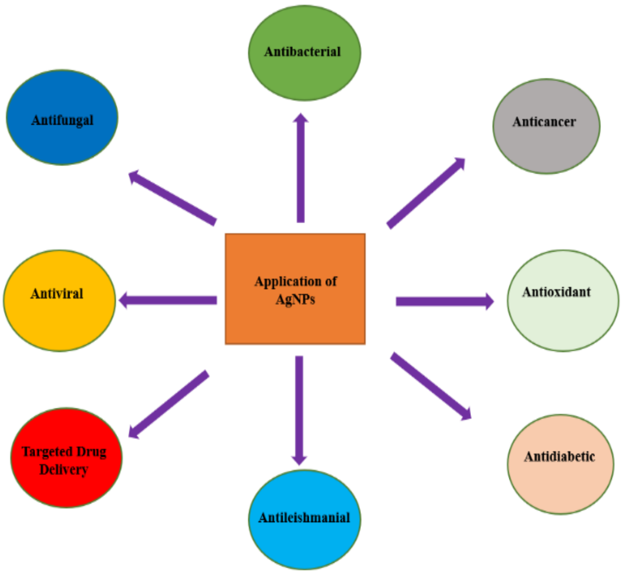

Fig 1. Summary and the possible biomedical applications of Ag NPs.

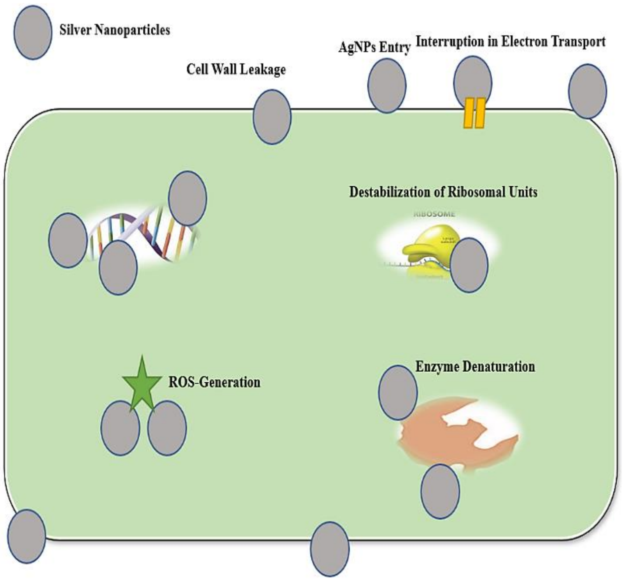

Fig 2. The proposed mechanism of the Ag NPs effect on bacterial cells.

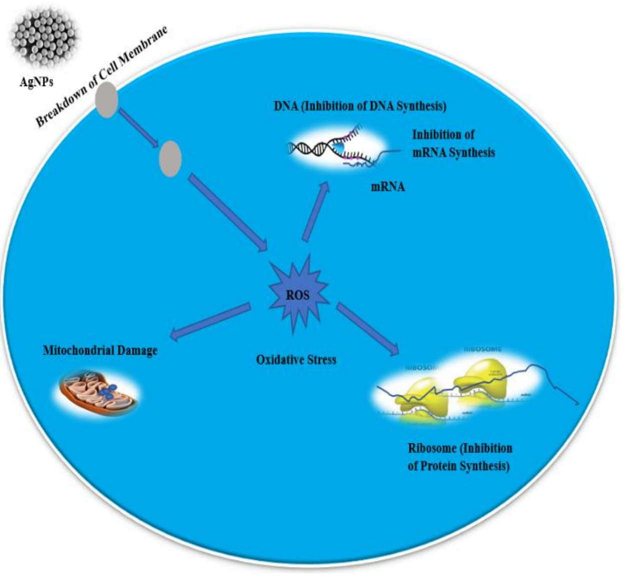

Fig. 3. Antimicrobial mechanism of Ag NPs.

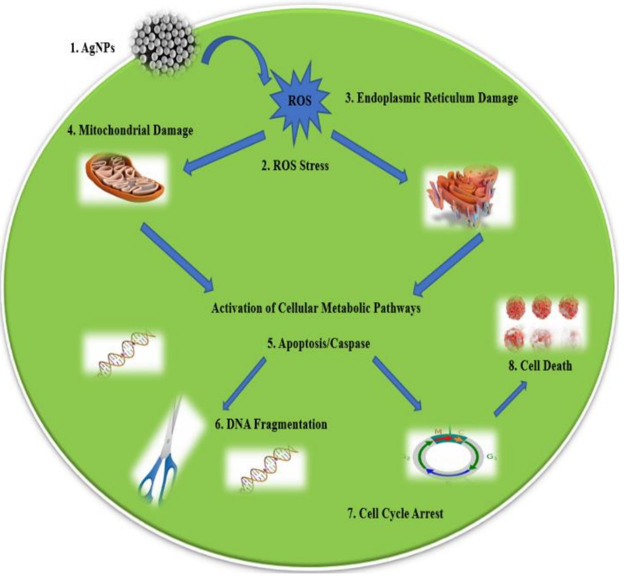

Fig 4. Anticancer mechanism of actions Ag NPs.

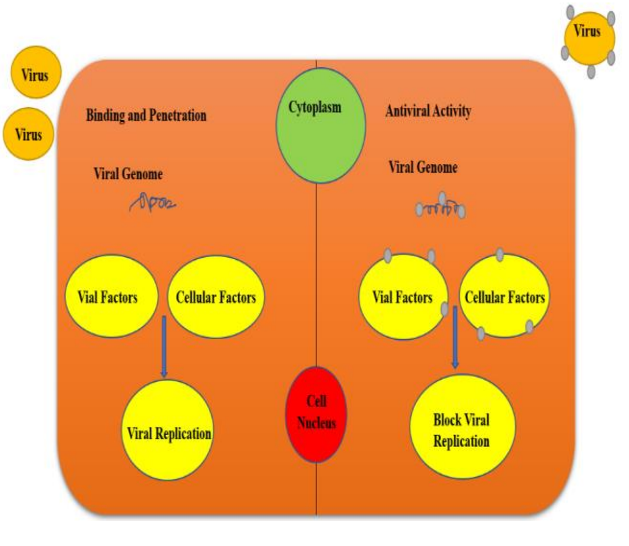

Fig 5. The mechanism of antiviral activity of Ag NPs.

Conclusion

The current review provides a comprehensive analysis of the synthesis, characterization, and biological applications of silver nanoparticles. Emphasis focuses on the antimicrobial and anticancer properties exhibited by these nanoparticles, as well as their mechanisms of action. Furthermore, the review explores the possible application of Ag NPs-based therapy techniques for cancer treatment. The potential application of Ag NPs as a novel anticancer therapeutic agent has already been explored in recent scientific and institutional research, because of the prominent unfavorable effects of chemotherapy and radiation therapy. Silver nanoparticles (Ag NPs) have attracted significant interest due to their unique properties and demonstrated flexibility across multiple disciplines such as textile, medicine, catalysis, biotechnology, nanotechnology, the field of optics electronics, and water purification. Nanoparticles (NPs) have been widely used as agents with anticancer and antimicrobial activities, including antibacterial and antifungal effects, throughout a variety of products. They exhibit significant inhibitory effects against microbial infections. Silver nanoparticles exhibit unique chemical, physical, optical, and biological characteristics as compared to other biomedical nanomaterials. Consequently, they possess the potential to serve as therapeutic platforms in diverse biomedical areas, including but not restricted to: (i) antiviral agents; (ii) antifungal agents; (iii) therapeutic agents for anticancer treatment; and (iv) antibacterial agents. The potential of AgNPs in the field of medicine is significant. However, prior to their practical use, it is important to carefully understand their effects, both advantageous and disadvantageous, on human health. Since it is important for silver nanotechnology to have efficacy in medical applications, it is necessary that the preparations of Ag NPs are simple, secure, effective, and environmentally friendly. Additionally, a more comprehensive understanding of safety control mechanisms, biodistribution, and pharmacokinetics must be acquired.

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