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"SILVER NANOPARTICLES IN CANCER THERAPY: GREEN SYNTHESIS, CHARACTERIZATION, AND MECHANISMS OF ACTION"

Jenanee Velayuthem V.*[1], Hemapriya V.[2], Dr. Anamika P. K.[3], Bala Vignesh K. S.[4], Akshaya B.[5] and Sruthika G.[6]

Assistant Professor, Department of Pharmacology, Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research.

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***Corresponding Author**
Jenanee Velayuthem V.
Assistant Professor, Department of Pharmacology, Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research.

ABSTRACT
The rapid advancement of nanotechnology has significantly contributed to the integration of nanoparticles in various biomedical applications. Among metallic nanoparticles, silver nanoparticles (AgNPs) are particularly noteworthy due to their distinctive physicochemical characteristics and relatively low toxicity. These nanoparticles can be synthesized through physical, chemical, or biological methods. Among these, the green synthesis approach is considered more cost-effective, sustainable, and less hazardous, owing to its environmentally friendly nature. To assess the functionality of silver nanoparticles, several characterization techniques are employed, including ultraviolet-visible (UV-Vis) spectroscopy, Fourier-transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), zeta potential analysis, scanning electron microscopy (SEM), and transmission electron microscopy (TEM). Research has demonstrated that when silver nanoparticles interact with cancer cells, they can induce oxidative stress, which may lead to mitochondrial dysfunction and ultimately cause DNA damage. This review highlights the green synthesis of silver nanoparticles using plant-based extracts and explores their potential mechanisms in cancer therapy.

KEYWORDS: Cancer therapy, Nanoparticles, Green synthesis, Silver, Plant extract.

INTRODUCTION

Silver has long been recognized for its potent antibacterial and antimicrobial properties. Historical records from the 18th and 19th centuries reveal its use in treating conditions such as epilepsy, ulcers, sore throats, and various ocular infections. With the advancement of nanotechnology, silver has been transformed into nanoscale particles—typically ranging from 10 to 100 nanometers—significantly enhancing its biomedical applications.[1] Initially, silver nanoparticles (AgNPs) were synthesized through physical and chemical methods. However, physical synthesis often demands high thermal stability, resulting in excessive energy consumption and low production yields.[2] Chemical synthesis, on the other hand, frequently relies on reducing and stabilizing agents that can produce hazardous by-products, posing significant environmental concerns.

In response to these limitations, green synthesis has emerged as a more eco-friendly and sustainable alternative. This approach employs biological entities—such as plant extracts, enzymes, and microorganisms—to facilitate nanoparticle formation.[3] Compared to other metal-based nanoparticles, AgNPs demonstrate relatively low toxicity toward mammalian cells and possess unique physicochemical properties.[4] They can also be synthesized in a variety of shapes, including spherical, rod-like, triangular, and octahedral forms.

Currently, silver nanoparticles are extensively used in catalytic applications, antimicrobial coatings for medical devices, and, most prominently, in cancer treatment. Their anticancer efficacy is largely attributed to their ability to induce reactive oxygen species (ROS), leading to oxidative stress and DNA damage in cancer cells. Consequently, numerous studies have investigated the cytotoxic effects of AgNPs on various cancer cell lines.[5] This review highlights the green synthesis of silver nanoparticles and explores their potential as therapeutic agents in oncology.

Synthesis of Silver Nanoparticles

Methods for the Synthesis of Silver Nanoparticles

Physical Synthesis	Chemical Synthesis	Biological Synthesis
• Laser ablation	• Sol-gel method	• Plant-mediated

• Evaporation condensation	• Co-precipitation	• Fungi-mediated
• Flash spray pyrolysis	•Microemulsion techniques	• Algae-mediated
• Ultrasonication		• Bacteria-mediated

In green synthesis, silver nanoparticles (AgNPs) have been successfully produced using a wide range of plant parts—including flowers,[6] seeds,[7] peels,[8] and leaves,[9]—as well as microorganisms such as bacteria, fungi, algae, yeast, and actinomycetes.[10] This biosynthetic approach leverages naturally occurring phytochemicals found in plant extracts—such as flavonoids, terpenoids, catechins, proteins, saponins, alkaloids, tannins, phytosterols, glycosides, phenols, and carbohydrates—which act as both reducing and capping agents to stabilize the nanoparticles. This method is not only cost-effective but also offers high yield with minimal environmental impact. Moreover, factors such as pH, temperature, and the concentration of silver salts significantly influence the size and morphology of the resulting nanoparticles.[11] and these parameters can be optimized depending on the intended application.

Step Wise Synthesis of Silver Nano Particles Explained in Figure-1

Plant material washed and converted to a coarse powder

↓

Extracted with a suitable solvent

↓

Plant extracts + silver salts

↓

Temperature, pH- maintained

↓

Reduction and capping of phyto constituents in plant extracts

↓

Green synthesized Silver Nanoparticles

↓

Separation by centrifugation method

↓

Characterization done by zeta potential, UV-VIS spectroscopy

↓

FTIR, SEM, TEM, X-ray Diffraction.

Fig 1. Synthesis of Silver Nano Particles.

Importance of Plant-Based Green Synthesis

- **Environmentally Safe**: No toxic by-products are produced in the process.[12]
- **Energy Efficient**: There is no need for extreme temperatures, high pressure, or hazardous chemicals.[13]
- **Enhanced Stability**: Plants typically generate more stable nanoparticles compared to traditional chemical or physical methods.[11]
- **Eco-Friendly**: The approach is environmentally sustainable and causes minimal harm to ecosystems.[12]
- **Cost-Effective**: It is an affordable alternative to other synthesis methods.[11]
- **Simple Process**: Special culture preparations or isolation techniques are not required.[13]

Characterization of Silver Nanoparticles

The characterization of silver nanoparticles is carried out using various techniques, including.

- **Scanning Electron Microscopy (SEM)**
- **UV-Visible Absorption Spectroscopy**
- **X-Ray Diffraction (XRD)**
- **Fourier Transform Infrared Spectroscopy (FTIR)**
- **Transmission Electron Microscopy (TEM)**
- **Zeta Potential Analysis**

Zeta Potential

- Zeta potential is a key physical property that reflects the surface charge of nanoparticles in a solution. It indicates the extent of electrostatic repulsion between particles, which helps to prevent agglomeration and ensures the stability of the nanoparticle dispersion. A higher zeta potential (ranging from ≤ +30mV to ≥ -30mV) suggests greater stability of the nanoparticles in suspension.[14]

- The measurement of zeta potential is crucial for evaluating the long-term stability of nanoparticles, particularly in colloidal solutions. It can be determined using a laser zeta meter. Proper preparation, such as centrifuging the mixture and washing with deionized water after sonication, ensures accurate and reliable results.[14,15]

UV-Visible Absorption Spectroscopy

- UV-Visible absorption spectroscopy is a fundamental technique used to analyze the formation, stability, and optical properties of nanoparticles. The absorption spectrum of nanoparticle solutions is recorded using deionized water as a reference.[16] After synthesis, the spectrum is immediately recorded within one hour to capture the initial characteristics of the nanoparticles. To assess the stability of the nanoparticles over time, the absorbance spectrum is monitored at intervals of 1 day, 15 days, and 30 days post-synthesis.[17]
- This method provides valuable insights into the stability and optical behavior of nanoparticles, helping ensure their suitability for various applications.[18]

FTIR (Fourier Transform Infrared) Spectroscopy

- FTIR spectroscopy is used to analyze the functional groups responsible for the reduction of silver ions into nanoparticles. This technique helps identify the functional groups involved in the bio-reduction process of silver nanoparticles.[19]

Scanning Electron Microscopy (SEM)

- Scanning Electron Microscopy (SEM) is used to examine the size, shape, and surface morphology of silver nanoparticles. This technique provides detailed high-resolution images that help assess the physical characteristics and distribution of nanoparticles, which is crucial for understanding their behavior in various applications.[20]

X-Ray Diffraction (XRD)

- X-ray Diffraction (XRD) is used to analyze the crystalline structure and molecular nature of silver nanoparticles. This technique provides valuable information about the crystal arrangement and allows for the determination of the nanoparticle size based on diffraction patterns. XRD is essential for confirming the crystallinity and phase composition of nanoparticles, which is important for their potential applications.[21]

Silver Nanoparticles in Cancer Therapy

- Silver nanoparticles (AgNPs) have shown significant potential in cancer treatment due to their ability to selectively target cancer cells.[4] Studies suggest that AgNPs can enter cancer cells through endocytosis and accumulate in the mitochondria. This interaction leads to the overproduction of reactive oxygen species (ROS), resulting in oxidative stress, mitochondrial dysfunction, DNA damage, and ultimately, cancer cell death.[5]
- The cytotoxic effects of silver nanoparticles are highly dependent on their size, with smaller particles generally showing greater impact on cell viability, ROS generation, and the activity of enzymes like lactate dehydrogenase, especially in breast cancer cell lines. Additionally, the toxicity of AgNPs is concentration-dependent and can vary across different cancer cell types.[4,5] Mechanism of action of Silver Nanoparticles in Cancer therapy as shown in Figure 2.
- Other influential factors include particle crystallinity, surface charge, and the type of medium used. Understanding these parameters is essential for optimizing the therapeutic efficacy of silver nanoparticles in cancer therapy.[22]

SOURCE	CELLLINE	SIZE	SHAPE	INHIBITORY CONCENTRATION$_{50}$ VALUE	DESCRIPTION
Ipomoea pes-caprae[23] 	MCF-7	50-100 nm	Spherical	78µg/ml	AgNPs could be an alternative chemotherapeutic as they showed Anti-proliferative action against MCF-7 cancer cell line
Quercusinfectoria[24] 	MCF-7	40 nm	Spherical	0.04 µg/ml	Silver nanoparticle in jaft extract showed the anti-proliferative effect

Fruit peel of  *Pomegranate*[25]	MCF-7	25 nm	Spherical shape	500µg/ml	Silver nanoparticle showed an anti-proliferative effect against the cancer cell line
Alternantherasessilis[26] 	MCF-7	10-30 nm	Spherical shape	3.04µg/ml	Approaching drug towards cisplatin, shoed cytotoxic effects
Piper nigrum[27] 	MCF-7 Hep-2	20-40nm	spherical	54 & 43 µg/ mL	Silver anoparticles cytotoxic effect shows against both the cell lines
Embelia Ribes[28] 	MCF 7	30.2 nm	spherical	62.5 µg/ mL	Green synthesized nanoparticles showed anti proliferative effect against MCF-7 cell line
Araucaria Heterophylla[29] 	MDA-MB-231	70-90 nm	spherical	75.29 µg/ mL	Silver nanoparticles showed dose-dependent cytotoxic effects against breast cancer cell line
Leaf extract of *Hydno Carpuspentandra*[30] 	MCF- 7	141-202nm (inter-particle distance)	Spherical	25 µg/ mL,50 µg/ mL, 100 µg/ mL	Silver nanoparticles increase cell viability showed Anti-proliferative effect against Breast cancer cell line
Flower extract of *Achillea biebersteinii*[31] 	MCF- 7	10-40nm	Spherical	20 µg/ mL	Silver nanoparticles caused dose-dependent decrease in cell viability, inhibited the proliferation in MCF-7 cancer cell line

Leaf extract of *Eclipta alba*[32] 	MCF-7	400-440nm	Spherical	10 µg/ mL	Silver nanoparticles inhibited cell proliferation of breast cancer cell
Leaf extract of *Portulacariaafra*[33] 	MCF-7	20nm	Spherical	75.40 µg/ mL	Green synthesized silver nanoparticles showed inhibitory activity in concentration dependent manner against cancer cell line (MCF-7)
Leaf extract of *Ailanthus excels*[34] 	MCF-7	20-30nm	Spherical	265.57 µg/ mL	Silver nanoparticles inhibits the protein synthesis of ribosomal peptide transferase leading to the termination of chain elongation in cancer cells
Cynara scolymus[35] 	MCF-7	220-223nm	Spherical	10 µg/ mL	Green synthesized silver nanoparticles showed a broad-spectrum anti-cancer activity with PDT therapy and hence promoted ROS generation by influencing mitochondrial apoptosis induction in MCF7 breast cancer cells.
Flower extract of *Scrophulariastriata*[36] 	MCF-7	10nm	spherical	52 ± 3.14 µg/ mL	Silver nanoparticles produced dose-dependent cytotoxicity against breast cancer cell line through activation of the ROS production and an increase in the intracellular Ca^{2+}
Leaf extract *Camellia sinensis*[37] 	MCF-7	10-30nm	spherical	20 µg/ mL	Silver nanoparticles showed Anti-proliferative action against MCF-7 cancer cell line.

Leaf extract *Tanacetum vulgare*[38] 	MCF-7	10 nm	spherical	5 µg/mL	*Tanacetum vulgare* extract induced AgNPs have exhibited dose dependant cytotoxic activity against MCF-7 cell lines.

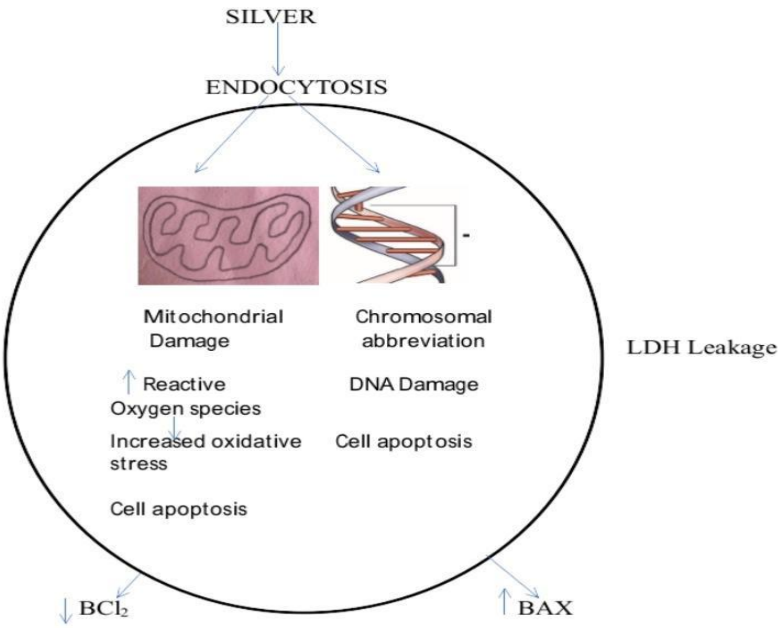

Fig 2. Mechanism of Action of Silver Nanoparticles in Cancer Therapy.[22]

CONCLUSION

Among various methods available for synthesizing silver nanoparticles, the green synthesis approach stands out as an environmentally friendly alternative, as it avoids the use of toxic chemicals. Characterization techniques play a crucial role in accurately identifying the structural and functional properties of these nanoparticles, ensuring they fall within the desired nanoscale range.[39]

Silver nanoparticles have demonstrated promising anticancer potential, particularly through their interaction with cancer cells. Upon entering the cells, silver ions tend to accumulate in the mitochondria and, to a lesser extent, in the nucleus. This accumulation increases the production of reactive oxygen species (ROS), which triggers apoptosis through multiple signaling pathways.[40]

These pathways are primarily associated with oxidative stress, mitochondrial dysfunction, and endoplasmic reticulum stress. Multiple in-vitro studies have confirmed the cytotoxic effects of silver nanoparticles on breast cancer cell lines. With continued research, silver nanoparticles hold great promise as a future tool in effective and targeted cancer therapy.[41]

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