

Emerging Trends in Silver Nanoparticle Therapies for Breast Cancer: A Comprehensive Review

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ABSTRACT

Breast cancer remains a ubiquitous malignancy affecting women across the world, especially in aggressive subtypes like triple-negative breast cancer and HER2-positive tumors. Although conventional modalities like chemotherapy and targeted monoclonal antibodies have improved outcomes, challenges including drug resistance and systemic toxicity persist. Recent advancements in nanotechnology, particularly the development of silver nanoparticles, have promising effects in cancer therapy due to their unique properties and targeted drug delivery. Silver nanoparticles possess potent anticancer activity through mechanisms such as oxidative stress, regulation of cellular metabolism, and targeted drug delivery through passive or active mechanisms. Eco-friendly green synthesis methods result in biological activities like anticancer, antibacterial, antiviral, and antifungal. This review highlights the delivery mechanisms of these AgNPs, emphasizing their emerging role as a novel and effective therapeutic option for breast cancer management.

Key words: Apoptosis, Breast Cancer, Drug Delivery, Ecofriendly, Silver Nanoparticle.

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INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among women and a dominant cause of mortality, with an estimated 310,720 new cases and 42,250 deaths anticipated in 2024 alone. The disease is classified into molecular subtypes, including Luminal A, Luminal B, HER2-enriched, and Triple-Negative Breast Cancer (TNBC). Nanotechnology offers advanced delivery systems that provide better stability, targeted delivery, and extended blood circulation compared to traditional methods. While few nanoscale systems like paclitaxel-albumin complexes are FDA-approved, research into metal nanoparticles like AgNPs continues to expand (Figure 1).

Numerous delivery systems are available, one of them is nanomedicine that have been used for drug delivery. It is more advantageous than traditional methods due to its targeted drug delivery system, stability and extended blood circulation (Fraguas-Sánchez *et al.*, 2025 and Fu *et al.*, 2025). Nanotechnology provides different systems or carriers that can deliver the drug

at targeted site. Despite extensive research in Pharmaceutical nanotechnology, the FDAs complete approval process has been successfully completed by just a handful of nanoscale drug delivery systems, including the landmark paclitaxel-albumin complex and sterically stabilized liposomal doxorubicin (Mugundhan *et al.*, 2024). The results of various studies are integrated into the thematic sections below: Types of Nanoparticles: NPs are classified into carbon, metal, ceramic, semiconductor, and polymeric types. Biological Activity: Plant-derived AgNPs (from leaves, seeds, or roots) show diverse activities, including antibacterial, anticancer, and antiviral properties.

Breast Cancer

Breast cancer is a worldwide risk with high death rates (Martínez-Sanmiguel *et al.*, 2024). Breast cancer exhibit significant molecular heterogeneity, with distinct classifications emerging from differential expression patterns of Hormone receptors and growth factor proteins. One subtype is Triple Negative Breast Cancer (TNBC), named due to lack of progesterone receptors, estrogen receptors and Human Epidermal Growth Factor Receptor-2(HER-2) which are commonly present in other breast cancers (Lehmann *et al.*, 2011). Most of the breast cancers are due to overexpression of the Human Epidermal Growth Factor Receptor 2(HER2) (Choong *et al.*, 2022). Monoclonal antibodies like trastuzumab had significantly raised the prognosis of patients for the patients with overexpression of HER2 (Chen *et*



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al., 2023; Vega-Rubín-De-Celis *et al.*, 2023). PYROTINIB, a small molecule has shown significant enhancement in both disease free and overall survival rates among the patients diagnosed with HER2 positive breast cancer¹². There are many adverse effects with the existing therapy and development of resistance due to genetic mutations. Therefore there are recent advances in cancer therapy with nanostructures like metal nanoparticles and these are available and can be formulated through a Eco-friendly environment to minimise the adverse effects with hazardous chemicals. Nanomaterials are approved as anticancer agents by the FDA. Nanoparticles are less toxic and can be used as Biomedicine (Liu *et al.*, 2023; Yazdi *et al.*, 2016).

Nanoparticles As Anticancer Agents

Nanotechnology has been a prominent field of research since late 20th century. Nanotechnology has enabled the creation of a wide variety of materials at nanoscale nanoparticles are one of those wide variety of materials (Khan *et al.*, 2019). Nanoparticle is defined as a particle with size less than 100 nm or ultrafine particle nanoparticles have different applications in various sectors ranging from carrier for drug to the target site and gene delivery into tumors. Nanomaterials differ from other bulk substances based on the size of the particle (Zahra *et al.*, 2020).

Types of Nanoparticles

Depending on physical and chemical properties nanoparticles have been classified as carbon NPs, metal NPs, Ceramics NPs, Semiconductor NPs, Polymeric NPs (Khan *et al.*, 2019).

Carbon Nanoparticles

Nanotubes and Fullerenes are the two major types of carbon based NPs. These Nanoparticles feature various attachment sites on their surface, which can be modified to connect with tissues, increasing their usage in targeted applications. Carbon nanotubes are essentially hollow, tube like structures formed by rolling a flat, single atom-thick layer of carbon atoms (Graphene) into a smooth, unbroken cylinder. These rolled sheets can be single sheet or double or multiple. If the sheets are single rolled, they can be called as Single Walled Nanotubes (SWNTs) and if they are multiple, they can be called as Multiple Walled carbon Nanotubes (MWNTs) (Bosi *et al.*, 2003; Pagona *et al.*, 2006).

Metal nanoparticles

Metal nanoparticles are prepared from the precursors of metals. Nanoparticles of metals such as copper, Silver, Gold have a broad range of absorption spectra. Metal nanoparticles have wide applications in research area (Khan *et al.*, 2019). These nanoparticles consist of a dielectric center coated with a nanoscale gold layer, forming a core shell spherical geometry. These nanoparticles possess unique optical and chemical features that enhance their performance in imaging and therapeutic biomedical applications (Hirsch *et al.*, 2006). Recently silver

nanoparticles have made to explore their properties and potential uses such as antibacterial and anticancer treatments (Chen *et al.*, 2009; Sun *et al.*, 2003). Silver Nanoparticle (AgNPs) possesses unstapped potential when compared to the relatively stable Gold Nanoparticles (AuNPs) (Desireddy *et al.*, 2013).

Ceramics Nanoparticles

Ceramic Nanoparticle is inorganic materials that have characterized porous nature and recently gained prominence as carriers for drug delivery (Cherian *et al.*, 2000). They have wide applications in catalysis, photodegradation of dyes etc. (Zahra *et al.*, 2020).

Semiconductor Nanoparticles

Semiconductor material contains both conductor and semiconductor properties and exhibit various applications. They play an important role in Photocatalysis, electronic devices (Khan *et al.*, 2019).

Polymeric Nanoparticles

These nanoparticles are derived from organic compounds and a distinct term called Polymer Nanoparticle (PNP) is used for it. Attaching polymers to proteins decreases immunogenicity extends plasma half-life and improve protein stability. By utilizing the enhancing permeability and retention effect, polymer-drug conjugates specifically accumulate in tumors and enable cellular level drug delivery after being internalized (Lee *et al.*, 2006). Importance of nanoparticles is because of their adaptable properties and their enhanced functioning or activity over their parent material. There are different methods of synthesizing the nanoparticles which may be hazardous and recent innovative using biological methods that are eco-friendly, safe and productive and this also called as green synthesis (Khan *et al.*, 2019).

Synthesis of Nanoparticles

Nanoparticles can be prepared by the three methods such as physical method, Chemical method and green method (Divya *et al.*, 2018; Hemmati *et al.*, 2020). Chemical methods used for the synthesis of silver nanoparticles have a common strategy of reducing and stabilising agents to monitor different sizes and different shapes for the targeted delivery and the toxicity of this chemical method is due to reducing agents. Methods that produce nanoparticles with high energy input are with reduced stability, which results in unwanted chemical reactions and agglomeration, thus unsuitable for *in vivo* drug delivery. Therefore the usage of toxic organic solvents hinder their application in drug delivery for lung and breast cancer. Correspondingly methods like UV- initiated photoreduction, irradiation and electrochemical synthesis need a lot of energy to make nanoscale particles. Even Tollen's method which uses carbohydrate still requires ammonia that results in toxic particles that makes them not entirely safe

for drug delivery (Malik *et al.*, 2018). Most of the studies are suggesting the use of green synthesis due to their use of nontoxic chemicals and low cost (Mescola *et al.*, 2017; Peter *et al.*, 2016; Castillo-Henríquez *et al.*, 2020). Green synthesis means the use of plant and fruit extracts as reducing and stabilizing agents. For example eco-friendly preparation using orange peel extract which contains polyphenols and polysaccharides act as reducing agents, carboxylic, amino acid and citric acid that act as stabilising agents (Skiba *et al.*, 2019). The most active constituent in orange is flavonoids that shows anticancer property (Tajaldini *et al.*, 2020).

Preparation of AgNPs and Ag/RGONCs

Silver nitrate, Graphene Oxide and extract of orange peel are necessary for nanoparticle formulation. Silver nitrate was dissolved in deionized water to obtain a 1 mM aqueous solution. 50 mg of Graphene oxide was dissolved in 100 mL of deionised water. A mixture was prepared containing 160 mL of silver nitrate solution, 20 mL orange peel extract, and 20 mL graphene oxide suspension, with continuous mild agitation. The reaction mixture was kept at dark conditions at room temperature for 12 hr and finally the obtained powder was dried at 90°C for at least 3 hr and ground into a fine powder for further characterization (Ahamed *et al.*, 2025). Table 1 shows the source and the activity exhibited by the nanoparticle.

Drug delivery system

Nanoparticles ranging from 1 to 100 nm have emerged as pivotal agents in the realm of drug delivery owing to their unique physiochemically properties and versatile functionality. These nanoscale constructs can be engineered to transport therapeutic

compounds with high specificity to designated biological targets. Their ability to markedly enhance pharmacological outcomes positions them as a cornerstone in the evolution of precision medicine. A fundamental challenge in the treatment of many pathological conditions lies in the targeted localisation of the therapeutic agents. Conventional formulations often suffer from suboptimal biodistribution, limited therapeutic index and poor selectivity, thereby compromising the clinical efficacy (Seleiman *et al.*, 2017) (Figure 2).

Advanced controlled release systems utilising nanoparticles enable site specific drug deposition, thereby maximising therapeutic impact on diseased tissue and minimising the systemic toxicity (KhademSadigh *et al.*, 2025). Nanoparticle mediated delivery has been categorised into five functional modalities, they are Diagnostic imaging, oncologic therapeutics, photosensitizer transport, nucleic acid delivery and protein-based interventions. Each modality harnesses the precision of nanotechnology to refine treatment accuracy, attenuate adverse effects and elevate clinical outcomes. Collectively these innovations are reshaping the landscape of contemporary medicine, particularly in the domains of molecular diagnostics and targeted therapeutics (Islam *et al.*, 2025). Targeted drug delivery system has been considered as favorable compatibility within the human systems. These systems effectively reduced the survival rates of breast cancer lines 4T1 and MCF-7, while showing the minimal toxicity towards endothelial cells. Additionally they exhibited potent anti-tumor activity in live animal models. Various polymer-based delivery platforms have been thoroughly explored for treating initial and advanced stages of breast (Salari *et al.*, 2022).

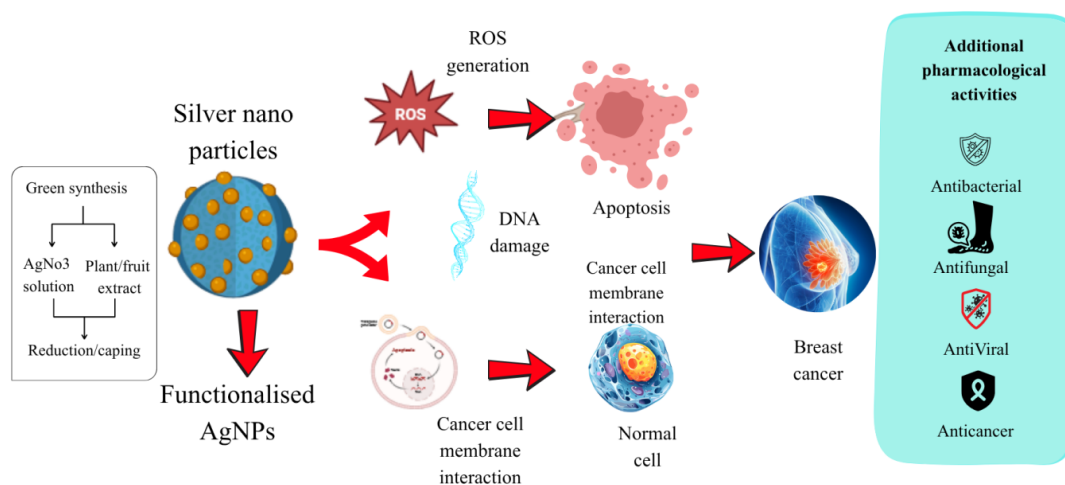


Figure 1: Mechanism of Silver Nanoparticles (AgNPs) (original image created with BioRender) The graphical abstract illustrates the mechanism of Silver Nanoparticles (AgNPs), including ROS generation, DNA damage, and apoptosis in breast cancer cells compared to normal cells.

Applications

From the advanced drug administration methods Nanoparticle drug delivery had been adopted as the most advanced method (Kuddushi *et al.*, 2025). The U.S Food and Drug administration has previously sanctioned multiple nanoparticle mediated chemotherapy platforms for breast cancer treatment, with numerous additional systems currently undergoing clinical evaluation. These drug delivery constructs based on polymeric nanocarriers, liposomal formulations, and paclitaxel loaded nanoparticles (Yang *et al.*, 2022; Zhou *et al.*, 2023). The Polymeric nanoparticles, in particular offer customizable surface architecture that can be engineered for permeability, biocompatibility and biodegradability. These carriers are synthesised using synthetic polymers or natural polymers. Their advantages include high drug encapsulation efficiency, scalable production and tunable release kinetics (Zhang *et al.*, 2024) PLGA (Poly(Lactic-Co-Glycolic Acid)) is a synthetic polymer has the ability to inhibit p-glycoprotein activity, a mechanism that plays a critical role in overcoming multidrug resistance. Nanoparticles are also employed in combination therapy approaches for breast cancer, where multiple therapeutic agents are co-delivered to achieve synergistic effects. This strategy has been shown to enhance the treatment outcomes, mitigate the emergence of drug resistance

and improve patient survival rates (Triantafyllakou *et al.*, 2022). While siRNA loaded nanocarriers have demonstrated promising therapeutic potential, their efficacy is still subject to the complexities of *in vivo* interactions. To better evaluate novel treatment modalities, patient derived xenograft mouse models are considered superior to conventional human breast cancer cell lines. These models retain the molecular, cellular, genomic and epigenomic characteristics of actual tumours, offering a more accurate platform for translational research (Wang *et al.*, 2024; Marinov *et al.*, 2025). The prism analogy aptly represents the multifaceted nature of nanoparticles, high lightening their ability to adapt and optimise drug delivery systems for specific pathological conditions. These innovations not only enhance drug bioavailability but also minimise systemic toxicity and elevate therapeutic efficacy (Islam *et al.*, 2025) (Figure 3).

Nanoparticle-driven advances in precision drug delivery

Nanotechnology enabled therapeutic delivery systems are revolutionizing modern healthcare by facilitating precise and efficient transport of bioactive compounds. These platforms enhance drug solubility, molecular stability and site specific targeting by leveraging the distinct physiochemical traits

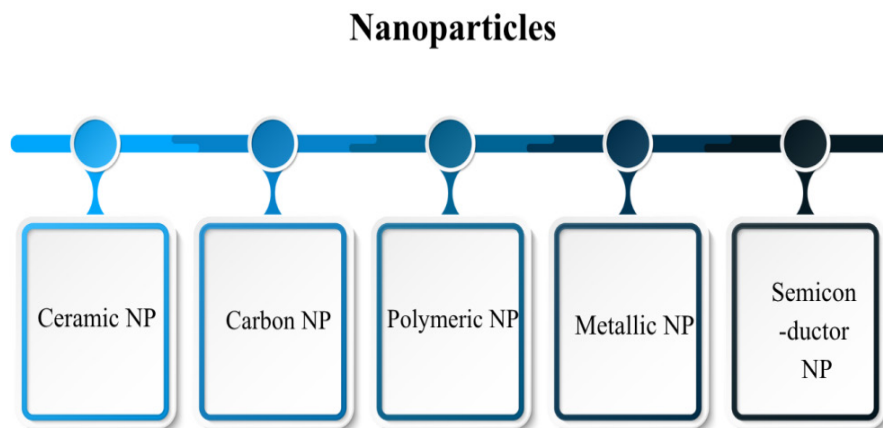


Figure 2: Types of Nanoparticles (original image created with BioRender).

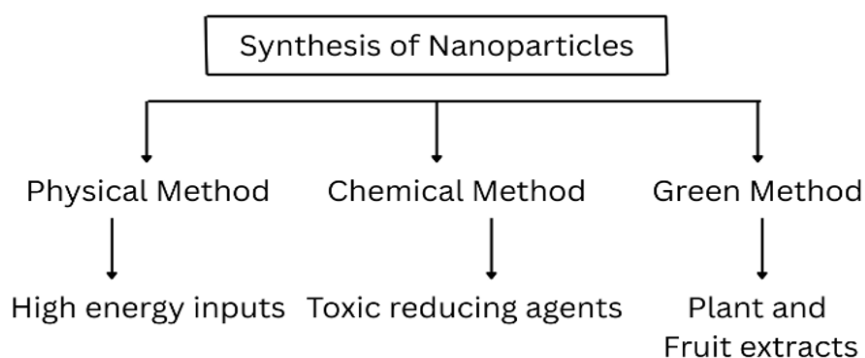


Figure 3: Flowchart of Methods of synthesis of nanoparticles (original image created with BioRender).

of nanomaterials such as high surface to volume ration, turnable surface chemistry and ultra small dimensions. Recent advancements focuses on engineering ecofriendly and physiologically compatible nanovehicles, including lipid based vehicles, polymeric nanostructures and inorganic nanosystems. Cutting edge surface engineering techniques and stimuli triggered release strategies are broadening their utility across diverse biomedical domains notably in immunomodulation, tissue regeneration and oncological therapies⁶⁰. The enhanced precision in targeting, regulating release profiles and improved dissolution and molecular stability provided by these nanocarrier systems significantly elevate the pharmacological availability of therapeutic agents. Moreover, their versatile drug - encapsulation potential enables the delivery of a broad spectrum of medicinal compounds while effectively navigating physiological barriers. These technological strides are paving the way for more refined and efficacious approaches to clinical drug administration (Tian *et al.*, 2021; Guo *et al.*, 2024).

1. Enhanced targeting efficiency,

2. Controlled drug release,
3. Improved drug solubility,
4. Versatility in drug loading,
5. Overcoming biological barriers.

Delivery of nanoparticles to cancerous cells

Nanoparticles are delivered to cancerous cells in two main ways i.e active and passive targeting. In active targeting (shown in Figure 4) nanoparticles are bind to specific receptors on cancer cells. These receptors are common on cancer cells than on normal cells. The receptors must be easily accessible and present in high enough numbers. Various molecules like antibodies peptides, nucleic acids, sugars and small vitamins can act as ligands for active targeting. Whereas passive targeting (shown in Figure 3) relies on the natural tendency of certain molecules to accumulate in tumors due to their leaky blood vessels and poor lymphatic drainage and this is known as EPR effect (Enhanced permeation and retention effect). When tumors grow beyond a certain size,

Table 1 : Source and the activity exhibited by the Nanoparticle.

Sl. No.	Plant Species	Parts of plant used for generation of nanoparticles	Size of nanoparticle	Shape of nanoparticle	Activity	References
01.	Youngia japonica, Melaleuca alternifolia and Aspiliaplurisetia	Leaf extract	Average size of 20 nm	Spherical shape	Antibacterial activity, Antifungal and antiviral, Antimicrobial properties	Ramadan <i>et al.</i> 2020
02.	Trigonellafoenum -graecum, Tectona grandis, Phoenix sylvestris, Phoenix dactylifera	Seeds	Diameter of 33.93 nm	Roughly spherical	Antibacterial, Anticancer, Antiviral, Antifungal, Antimicrobial	Varghese <i>et al.</i> 2019
03.	Chlorophytum borivilianum	From Flowers	Diameter of 52 nm	Roughly spherical	Antimicrobial	Huang <i>et al.</i> 2019
04.	Dorema ammoniacum	Stem	Average size of 15 nm	Roughly spherical	Antibacterial	Zandpour <i>et al.</i> 2018
05.	Zingiber officinale, Butea monosperma, Syzygium cumini, Diospyros montana	From Bark	13 nm diameter	Spherical	Antibacterial	Yang <i>et al.</i> 2017, Das <i>et al.</i> 2018
06.	Allium fistulosum, Lepidium draba, Angelica pubescens, Arctium lappa	Roots	Average size of 5 nm	Spherical	Antibacterial, Antifungal activity	Benakashani <i>et al.</i> 2017, Markus <i>et al.</i> 2017
07.	Sida cordifolia, Sida acuta, Elaeagnus umbellata, Rheum ribes	Whole plant	Average size of 50 nm	Spherical	Antibacterial	Aygün <i>et al.</i> 2019, Seleimanet <i>al.</i> 2003

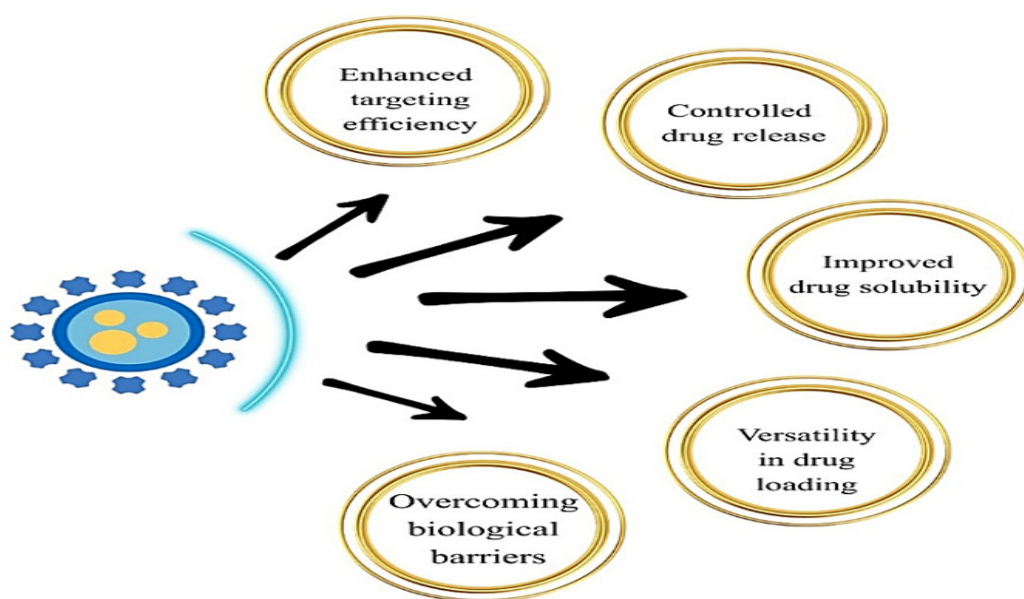


Figure 4: Nanoparticle Drug delivery systems (original image created with BioRender).

they don't get enough oxygen causing some cells to die and new blood vessels to form. This allows nanoparticles to enter and stay in tumor (Malik *et al.*, 2018).

PHARMACOLOGICAL ACTIVITIES OF NANOPARTICLES

Antibacterial Activities

Metallic nanoparticles exhibit antibacterial property by disrupting the cell membrane and inhibition of protein synthesis (Sondi and Salopek-Sondi, 2004). Higher the concentration of nanoparticles higher the membrane permeability into the bacteria (Kasthuri *et al.*, 2009). Silver nanoparticles are biosynthesized by a single step process using *Citrus sinensis* peel extract which act as reducing agent. These nanoparticles are active against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (Kaviya *et al.*, 2011).

Antifungal Activity

The Silver nanoparticle derived from plants have demonstrated evident membrane damage in *Candida* species as well as disruption of fungal intracellular components ultimately leading to the destruction of cell function (Logeswari *et al.*, 2025). Antifungal agents are associated with significant adverse effects, including hepatotoxicity and nephrotoxicity. The fungal cell wall is composed of a dense polymeric structure primarily made up of lipids and proteins. The silver nanoparticles have multifunctional activities against the fungus and disrupt the growth of fungal cells (Gardea-Torresdey *et al.*, 2002).

Anti-Plasmodial Activity

The metallic silver nanoparticles efficiently control the malarial production. Active constituents like quinine, artemisinin and

aromatic compounds used against resistant strains of malaria parasites (Jayaseelan *et al.*, 2011).

Anticancer Activity

Cancer is the uncontrolled division of cells. This uncontrolled cell cycles can be disrupted using bio-based nanoparticles. Metallic nanoparticles are effective against different types of cancerous cells like Hep 2, HCT 116, and HeLa cell lines (Raghunandan *et al.*, 2011). Nanoparticles help in regulating the production of free radicals. Free radicals offer trigger cell proliferation and disrupt the normal cellular functions. This oxidative stress led to significant damage in biological systems affecting the integrity and stability of cells (Dipankar *et al.*, 2012). Similarly, treatment of the MCF-7 cancer cell line with silver nanoparticles has maintained the concentration of biomolecules within the cells leading to regulation of cell metabolism (Das *et al.*, 2011). Metallic nanoparticles consist of innovative implementations in aiding diagnosis and treatment of different types of cancers and retroviral diseases. The advent of biologically synthesized nanoparticles marks a step forward, offering the ability to target malignant deposits effectively while sparing normal cells from the damage (Suman *et al.*, 2013).

Antiviral Activity

Bio-based nanoparticles have a promising alternative for treating and controlling the viral pathogens. These metallic silver nanoparticles serve as a potent broad spectrum antiviral agent, prevent the entry of viral pathogen into the host cell. These nanoparticles possess multiple binding sites that attach to gp120 of the viral membrane and act as virucidal.

The results of various studies are integrated into the sections below: Types of Nanoparticles: NPs are classified into carbon,

metal, ceramic, semiconductor, and polymeric types. Biological Activity: Plant-derived AgNPs (from leaves, seeds, or roots) show diverse activities, including antibacterial, anticancer, and antiviral properties.

CONCLUSION

Employing silver nanoparticles in biomedical research represents a cutting-edge development for aggressive breast cancer subtypes. Their unique physiochemical properties, such as high surface area and the ability to generate reactive oxygen species, allow AgNPs to offer enhanced therapeutic efficacy with lower systemic toxicity compared to conventional therapies.

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ABBREVIATIONS

AgNPs: Silver Nanoparticles; **HER2:** Human Epidermal Growth Factor Receptor-2; **TNBC:** Triple-negative breast cancer; **FDA:** Food and Drug Administration; **ROS:** Reactive Oxygen Species; **PLGA:** Poly(lactic-co-glycolic acid); **EPR:** Enhanced permeation and retention effect; **siRNA:** Small interfering RNA; **AuNPs:** Gold nanoparticles; **SWNTs:** Single Walled Nano Tubes; **MWNTs:** Multiple walled carbon nanotubes; **PNP:** Polymer Nano Particle; **RGONCs:** Reduced Graphene Oxide Nanocomposites.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Nanoparticles act as multifunctional vehicles that revolutionize healthcare by facilitating precise transport of bioactive compounds, improving drug solubility, and navigating biological barriers to elevate clinical outcomes.

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