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Review Article

Silver Nanoparticles in Combination Cancer Therapy: Enhancing Efficacy and Overcoming Resistance

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Abstract

The physicochemical properties peculiar to silver nanoparticles, AgNPs, including a considerable surface area, their ability to adjust in size, and facile functionalization, have attracted further interest in the oncology field since they can be used to treat cancer specifically and promote synergistic effects when used in combination therapies. The latest advancements in synthesis, functionalization, anticancer mechanism of action, and the combination of AgNPs with immunotherapy, radiotherapy, chemotherapy, photothermal therapy, and photodynamic therapy are comprehensively summarized in this review, which covers the period up to 2025. Methods for improving stability and biocompatibility, as well as tumor specificity, can be observed in discussions of physical, chemical production pathways, as well as green/biogenic production pathways. AgNPs mechanistically elicit anticancer effects through the production of reactive oxygen species (ROS), mitochondrial dysfunction, DNA damage, cell-cycle arrest, anti-angiogenesis, and alteration of the tumor immunologic microenvironment. When used in combination with multimodal regimens, preclinical and emerging clinical trials indicate an increase in efficacy and an ability to reverse drug resistance; however, questions on safety remain that including normal cell toxicity, fluctuating biodistribution, and accumulation. To minimize off-target consequences, prospects emphasize the need to use a synchronized synthesis method, dose control, and advanced targeting methods. Combination therapies based on AgNP are becoming a potential future trend in the modern use of cancer drugs due to the fact that they fit in the gap between nanotechnology and oncology and are likely to become an important part of increasing intervening effects, curing cancer resistance, and creating a path to individualized cancer care.

Keywords: Silver Nanoparticles; Combination Cancer Therapy; Reactive Oxygen Species; Drug Resistance Reversal; Radio Sensitization; Immunomodulation; Photothermal Therapy; Photodynamic Therapy; Targeted Drug Delivery; Nanomedicine

Introduction

Although the current methods in cancer diagnosis and treatment have been improving, cancer remains a major cause of mortality around the world, and its occurrence, as well as healthcare expenditure, is continuing to increase [1]. Even though patient survival has improved with traditional modes such as chemotherapy, radiation, and targeted drugs, heterogeneity of the tumor, off-target effects, and the development of drug resistance tend to restrict their efficacy. The combination cancer therapy, involving the use of two or more forms of therapeutic approaches, has emerged as an attractive paradigm to overcome the challenges [2]. It enables synergetic effectiveness, low doses of each agent, and reduced chances of an emergence of resistance. Against this backdrop, the silver nanoparticles (AgNPs) have been attracting a lot of attention in 2025 because they are effective and versatile adjuncts to old and new cancer treatments [3]. Their unique physicochemical characteristics, such as significant surface-area-to-volume ratio, surface chemistry tunability, and intrinsic cytotoxicity against malignant cells, enable many modes of action, among which one might include the generation of reactive oxygen species (ROS) and mitochondrial dysfunction, induction of DNA damage, and modulation of the tumor microenvironment [4]. Recent studies have demonstrated that they can enhance the outcomes of phototherapy, kill cancerous cells with a resistant status, and act in combination with bioactive compounds to induce cell cycle and apoptosis. Moreover, the AgNPs can be designed to deliver photosensitizers, phytoconstituents, or chemotherapeutic drugs with controlled release in specific tumor sites [5]. AgNPs are being touted as valuable components of multimodal regimens such as photodynamic therapy, photothermal therapy, and chemo-phytochemical combinations due to both their direct cytotoxic and augmentative therapeutic properties [4]. The goal of the review is to critically summarize the latest information on AgNP-based combination cancer therapy in 2025 and focus on the translational value of treatment, its preclinical confirmations, and its molecular basis. This paper aims to show the role of AgNPs in guiding the future, high-precision oncologic care by evaluating the current progress toward optimization, decreasing side effects, and overcoming multidrug resistance [5].

Synthesis and functionalization of silver nanoparticles

The production and functionalization of silver nanoparticles (AgNPs) can be roughly classified into three categories, namely, physical, chemical, and green or biogenic, depending on what properties of the particle are desired and how the particle is to be applied [6]. Every one of the approaches enjoys its advantages and shortcomings. Physical methods, employing a top-down strategy, involve the application of high-energy processes, including laser ablation, evaporation-condensation processes, arc discharge, and spray pyrolysis, to decompose bulk silver so as to generate nanoscale particles [7]. Evaporation and condensation involve the burning of large amounts of silver in a furnace, followed by a swift quenching to make nanosized particles, whereas in laser ablation, concentrated laser beams are used to ablate a silver target, and the silver particles are formed by evaporation in a substance that leaves only pure nanoparticles having no chemical or impurities [8]. Such processes are energy-intensive, require special equipment, often give broad particle size distributions, yet can often yield high-purity products and obviate the use of chemical reagents. Chemical synthesis methods, instead, adopt a bottom-up approach, in which silver ions are reduced by direct reduction reactions to form nanoparticles [9]. The common pathways are microemulsion techniques, where nanoscale droplets in the systems using surfactant, which serve as a confined reactor, result in a larger control of size and also shape, chemical reduction with reductants such as sodium borohydride or citrate that favour rapid nucleation and growth of AgNPs [10]. In spite of the fact that they still may need purification after synthesis and introduce dangerous reagents, other chemical methods, such as electrochemical deposition, microwave-assisted synthesis, and photochemical reduction, have their benefits, such as faster reaction, improved uniformity, or milder conditions. Due to their environmentally friendly nature, green and biogenic methods of synthesis of AgNPs, through the enzymatic systems, microbial cultures, or plant extracts, as they simultaneously stabilize and reduce the AgNPs, have attracted significant attention [11]. Whereas metabolic processes or enzymes secreted by microbes and fungi precipitate the silver ions into nanoparticles, in plant-mediated synthesis, phytochemicals such as flavonoids, phenolics, and proteins are used as both reducing and capping agents. Any of these synthesis routes may be modified to inject functionalization of AgNPs through surface modification with biomolecules, polymers, or selective attachment of targeting ligands in order to impart stability, biocompatibility, and specificity to the process in biomedical applications [12]. The selection of the synthesis method is very important to fine-tune AgNPs against therapy requirements. Enzymatic synthesis and other biological approaches offer high degrees of control over the morphology of the particles at mild conditions and are cost-efficient, scalable, and environmentally benign, but may be affected by variability since the biological origin is different and synthesis rates are slower [13] (Figure 1).

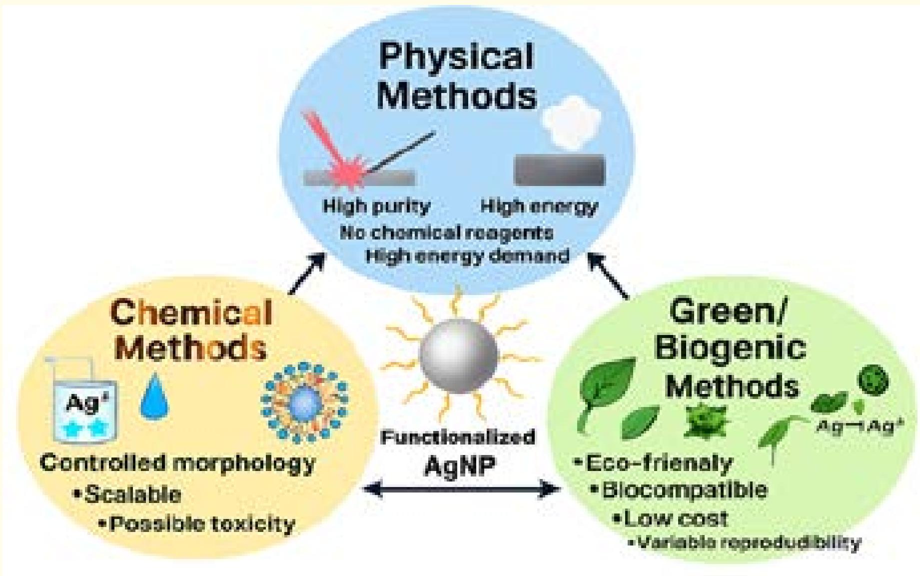

Figure 1: "Synthesis Routes for Silver Nanoparticles: Physical, Chemical, and Green/Biogenic Approaches".

A schematic representation of three distinct synthesis approaches for silver nanoparticles: Physical (light blue), Chemical (light orange), and Green/Biogenic (light green). Each panel highlights key visual elements and attributes of the method, converging toward a central functionalized AgNP. The nanoparticle is depicted with surface ligands, symbolizing its biomedical relevance. Arrows from each route emphasize that all methods can lead to functionalized AgNP formation.

Mechanisms of anticancer action of AgNPs

Through a network of interconnected routes, silver nanoparticles (AgNPs) possess potent anticancer action that directly and indirectly targets cancerous cells through the tumor microenvironment, with such effect directly modulated by the nanoparticles. The most famous process is the formation of reactive oxygen species (ROS) [14]. It starts when AgNPs get inside cells, mainly by endocytosis, and then eliminate silver ions (Ag+), which trigger redox processes. This higher burden of ROS production overwhelms glutathione and other antioxidant defense mechanisms and leads to oxidative stress and damage to proteins, lipids, and nucleic acids. Most vulnerable to it are tumor cells that are high on the list of oxidative stress [15]. It may lead to lipid peroxidation, protein carbonylation, as well as unlock the stress responding signal pathways such as p38 MAPK and JNK that promote apoptotic signalling. Excessive production of ROS also has adverse effects on mitochondria, which are a crucial controller of intrinsic apoptosis. AgNP-induced oxidative stress causes structural damage such as disorganization of cristae, opening of permeability transition pore, and disruption of mitochondrial membrane potential [16]. Due to these processes, pro-apoptotic proteins, such as cytochrome c, enter the cytoplasm, triggering the activation of caspase-9, and subsequently caspase-3, which induces apoptosis. At the same time, the expression of proteins of the Bcl-2 family is also changed by AgNPs by overexpressing the proteins of Bak and Bax and down-regulating the proteins of Bcl-2 and Bcl-xL, which gives a tilt towards programmed cell death [17]. Examples of genotoxic outcomes of oxidative stress and direct contact of Ag+ with nuclear constituents include DNA base oxidation, single- and double-strand breaks, and crosslinking. The lesions induce DNA damage response, including but not limited to ATM/ATRp53-mediated cell cycle arrest at the G1/S or G2/M checkpoints by suppressing cyclin B1 and CDC2. Repair is prevented by arrest and leads, in the failure case, to apoptosis [18]. AgNPs possess anti-angiogenic activity beyond tumor cell killing due to working along the vascular endothelial growth factor (VEGF) pathway that is fundamental in new blood vessel development. They inhibit the migration, proliferation, and tube formation of endothelial cells by suppressing the levels of VEGF and its receptor VEGFR-2 in endothelial cells, as well as downstream of the PI3K/Akt and ERK1/2 signalling. Besides, AgNPs suppress the activity of matrix metalloproteinases (MMP-2 and MMP-9) as extracellular matrix breakdown requires the presence of these metalloproteinases. This essentially cuts off the blood and nutrient supply to tumors [19]. An additional critical immunomodulatory potential of AgNPs is to rewire the tumor microenvironment (TME) to facilitate an antitumor immune response. They are able to boost the action of canonical T lymphocytes (CTLs) and natural killers (NK) and reduce the number of immunosuppressive cells, e.g., regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). AgNPs also promote M1 polarization along with the subsequent production of pro-inflammatory molecules and tumoricidal effects, such as NF-κB and augmented amounts of TNF-α and IL-12 renewal [17]. They are also taken by cancer patients to limit the infection risk in an impaired state due to their antibacterial effect. Together with the activation of tumour-associated fibroblasts and changes of extracellular matrix structures, the immune-mediated effects of functionalizing AgNPs with immunostimulatory molecules or checkpoint inhibitors can be augmented and can help direct immune cell infiltration [20]. Angiogenesis inhibition, mitochondrial and DNA damage, with arrest of cell cycle, production of oxidative stress, and immunological modulation all serve together to create a multifaceted assault against tumor survival, flexibility, and metastatic capacity. In situations where AgNPs are incorporated in combination regimes with chemotherapy, radiation, phototherapy, or immunotherapy, the multimodal effect of this approach decreases the risk of resistance development and increases the efficacy of such therapy [21]. AgNPs present an opportunity to develop next-generation precision oncology due to their ability to be tailored to optimal tumor targeting and low (or negligible) off-tumor collateral damage by controlling size, surface chemistry, and targeting ligands (Figure 2).

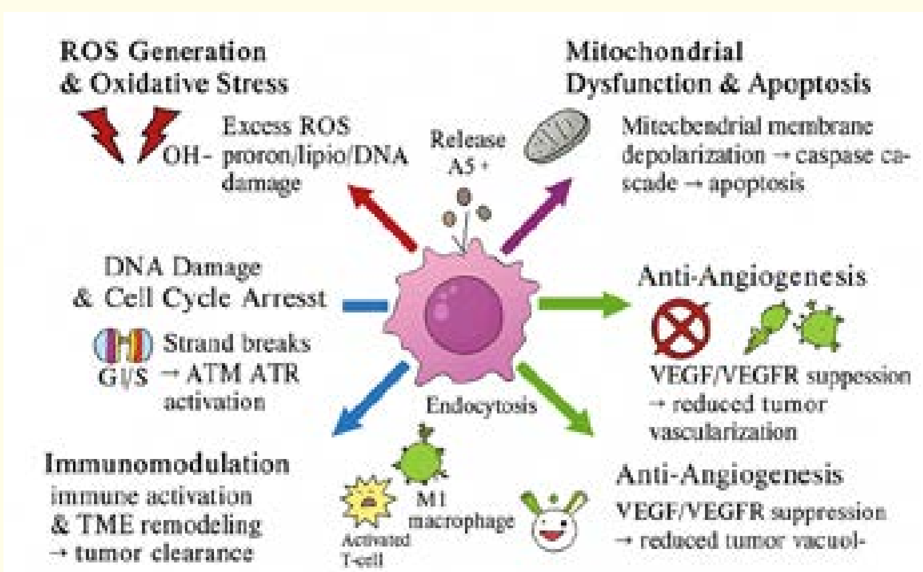

Figure 2: Integrated Mechanisms of Silver Nanoparticles in Cancer Therapy.

Silver nanoparticles (AgNPs) exert anticancer effects via five key mechanisms: ROS generation, mitochondrial dysfunction, DNA damage, anti-angiogenesis, and immunomodulation. Each pathway converges on a central tumor cell, with AgNPs entering via endocytosis and releasing Ag^+ ions to initiate therapeutic actions.

Silver nanoparticles in combination therapy approaches

Silver nanoparticles (AgNPs) enhance the therapeutic capacity of chemotherapy, radiation, immunotherapy, photothermal therapy (PTT), photodynamic therapy (PDT), and multimodal methods and thus have emerged as very effective add-ons to cancer therapy [22]. Due to high surface-to-volume ratio and ease of functionalization, AgNPs make excellent drug carriers in synergistic drug delivery combination therapies that rely on chemotherapy. This enables encapsulation in stimuli-responsive nanocarriers or conjugation of chemotherapeutic agents. The systems help the accumulation of drugs intracellularly by bypassing efflux transporters and obstructing their functions, allowing controlled and selective drug release at the sites of the tumor and helping to combat multidrug resistance (MDR) [23]. Given the potential to deplete intracellular glutathione and disrupt ATP-binding cassette transporters, AgNPs also showed promise at enhancing the sensitivity of cancer cells to chemotherapy agents such as doxorubicin, cisplatin, and paclitaxel [24]. AgNP administration is enhanced through attachment of cell-penetrating peptides or specific ligands, further selectivity in the targeting of cancerous tissue. AgNPs are also effective radiosensitizers in radiotherapy due to enhancing radiation-induced oxidative stress levels and increasing the production of reactive oxygen species (ROS), damaging the DNA, proteins, and cell membranes [25]. They have a high atomic number compared to other substances; thus, they can effectively interact with ionizing radiation, thereby raising DNA double-strand breaks and generating secondary electrons. AgNPs also enhance radiosensitivity through inhibition of the cells' antioxidant defence mechanism. Smaller AgNPs and particularly 20-50 nm, have been reported to be more effective at tumor cell radio sensitization, most notably in glioma, gastric, breast, lung, and hepatocellular carcinoma cells. It has also been tested i*n vivo* and has been proven useful that these AgNPs enhance tumor regression and survival advantages when combined with radiation therapy [26]. Also, when used in an immunupdateul manner, AgNPs can trigger immunogenic cell death (ICD) characterized by accumulation of ATP, exposure to calreticulin, and release of high-mobility group box 1 (HMGB1). This treatment procedure primes cytotoxic T-cells and enhances antigen presentation, making it easier to treat with immune checkpoint blockade (ICB) therapy using drugs such as PD-1 or CTLA-4 treatment. AgNPs also can modify the tumor microenvironment, which supports immunotherapeutic interventions, such as pro-inflammatory cytokine production, draw dendritic cells, and enhance CD8+ T cell infiltration into tumor tissues. When used with PTT and PDT, AgNPs demonstrated the ability to convert near-infrared (NIR) light energy to local heat [27]. This leads to ROS and hyperthermia, which directly kill cancer cells and even increase drug ingestion and disrupt the tumor vasculature. The on-demand drug release induced by the incorporation of AgNPs into photo responsive nanocarriers allows regaining control throughout treatment both temporally and spatially, as well. Photothermal effects may also liberate antigens associated with the tumor in addition to destroying the initial tumors, preventing the recurrence process by provoking the immune system [28]. AgNPs have the potential to enhance singlet oxygen generation and cytotoxicity during PDT, both by carrying photosensitizers and enhancing the photophysical properties of other photosensitizers used in combination. Such combinations as the chemo-PTT-immunotherapy, radio-PTD-chemotherapy, or the PTT-radiotherapy make use of the unique multifunctional nature of AgNPs and aim at tumor targeting using diversified synergistic effects [29]. It is a new area in that AgNPs are being integrated into multi-modal therapeutic platforms. As an example, the triple-modality systems can enhance the clearance of a tumor and provide further immune surveillance in the long term because they deliver chemotherapeutics, cause local hyperthermia in response to NIR irradiation, and stimulate immune activation [30]. The studies conducted on various metallic nanoparticles demonstrated that it is possible to combine immunomodulation, photothermal ablation, and radio sensitization on a single platform and thus significantly restrict tumor growth, prevent the spread of metastases, and reduce cases of recurrent cancer [31]. AgNPs have inherent antimicrobial properties, biocompatibility after proper surface modification, and can be designed through biodistribution and targeted delivery in tumors through the enhanced permeability and retention (EPR) effect, or active targeting offers a special promise towards such designs [32]. Thus, AgNPs can significantly enhance traditional cancer treatments by enhancing drug delivery effectiveness, inverting resistance mechanisms, radio sensitization, activating those tumors that are resistant to normal therapy, triggering anti-tumor immunity, developing light-responsive cytotoxicity, and giving a multifaceted scaffold where multiple modalities can be integrated [33]. The future development of oncological therapeutic capabilities, focused on diminishing the systemic toxicity, enhancing the activity of drugs, and overcoming the instrumental clinical issue, whereby therapy-refractory cancers emerged, would be based on the combined advantages of AgNPs [24].

Preclinical and clinical studies of silver nanoparticles in cancer therapy

After a careful assessment of the preclinical model, silver nanoparticles (AgNPs) are now in the process of shifting to clinical application in oncology. Preclinical studies have demonstrated that AgNPs possess potent cancer-killing action involving the process of DNA damage, mitochondrial dysfunction, ROS-induced apoptosis, and variation in the tumor microenvironment [34]. Significant concentration- and size-dependent cytotoxicity has been exhibited by *in vitro* investigations at various cancer cell lines, such as breast cancer, lung cancer, liver cancer, cervical cancer, and glioma, with the functionalized AgNPs providing amplified selectivity and less toxicity with regard to normal cells [35]. *In vivo* experiments in murine tumor models have confirmed a drastic decrease in tumor volumes as well as inhibited metastasis when AgNPs were administered alone or in combination with chemotherapy, radiation, and photothermal therapy [36]. On the surface level, PEGylation, antibody conjugation, and biogenic coating have been shown to boost pharmacokinetics and targeted distribution. AgNPs have primarily reached the stage of early-phase clinical trials in the field of antibacterials and wound healing, although novel cancer-targeted studies are investigating safety, biodistribution, and possible use as drug or gene delivery vehicles [37]. The safety profiles regarding initial therapeutic levels indicate that they are tolerable; however, other factors, such as accumulation and, that is, long-term toxicity, are also of concern. To maximise efficacy and minimise systemic exposure, synthesis, stability, and selective distribution are optimised during the ongoing process of moving a technology from preclinical use through to clinical use [37] (Table 1).

Table 1: “Summary of Preclinical and Clinical Studies on Silver Nanoparticles in Cancer Therapy”.

St Table udy Type	Cancer Model/Patient Type	AgNP Formulation	Key Findings
Preclinical (*in vitro*)	MCF-7 breast cancer cells	Citrate-coated AgNPs	Dose-dependent cytotoxicity via ROS generation
Preclinical (*in vivo*)	Murine melanoma	PEG-AgNPs + doxorubicin	Enhanced tumor regression, reduced toxicity
Clinical (Phase I)	Solid tumor patients	AgNP drug carrier	Safe at tested doses, ongoing efficacy evaluation

Safety, toxicity, and pharmacokinetics

Even though silver nanoparticles (AgNPs) have substantial anticancer activity, they raise concerns about pharmacokinetics, safety, and toxicity; all important aspects of clinical translation. Cytotoxicity to normal cells is a major disadvantage because AgNPs can induce oxidative stress, membrane leakiness, and apoptosis in healthy tissue and especially during high concentrations or following prolonged exposure [24]. Due to their non-specific distribution, off-target effects may include hepatotoxicity, nephrotoxicity, and neurotoxicity. Pharmacokinetic studies have shown that particle size and shape, surface charge, and coating also influence the way AgNP is distributed in the body; large-sized particles have the potential to be deposited in the liver, spleen, and kidneys, whereas smaller particles (smaller than 10 nm) often enter biological barriers more readily [38]. The primary clearance pathways include the reticuloendothelial system and renal clearance; however, even minor ineffective clearance can lead to eventual tissue distribution [39]. To minimize systemic toxicity in combination therapy, surface modification (e.g., to biocompatible polymers, such as PEG) as well as conjugation to target tumor-specific ligands (antibodies or peptides) should also be considered, not to mention release mechanisms that hinder drug leakage. The toxicity can be further reduced by using biogenic or green-synthesised AgNPs in order to augment biocompatibility [39]. Dose adjustment, real-time biodistribution imaging, and comprehensive toxicological evaluation are, however, important in order to balance the therapeutic efficacy and safety. Design of AgNP formulations should be well planned in such a way that it confers an optimum anticancer activity and low systemic adverse impact [40].

Challenges and future perspectives

Applying silver nanoparticles (AgNPs) practically in the treatment of cancer is full of challenges, despite some remarkable achievements [41]. The problem lies in the possible cytotoxicity to other healthy tissues, a lack of understanding regarding long-term biodistribution, and concerns with bioaccumulation, which is known to potentially lead to chronic toxicity [42]. Synthesis technique variability is negatively affecting regulatory approval, in addition to stability, scale, and reproducibility [43]. It continues to be challenging to optimize the dosage ratio and administration schedule of a combination medicine to ensure its unique formulation produces a synergistic effect without an accompanying augmentation of toxicity. Besides, evidence-based risk-benefit assessments are limited by the insufficient clinical information regarding AgNP-based cancer therapies [44]. Research moving forward needs to focus on the development of green and economic procedures that are uniform in terms of synthesis procedure; advanced targeting methodologies, such as stimuli-sensitive release and ligand conjugation, and application of artificial intelligence to predict the most optimal formulations and dosage levels [45].

The extension of clinical trials, with severe clinical safety monitoring, will be necessary to validate the results of the preclinical study and see the importance of evidence-based registered nurses. AgNPs can become a critical part of multimodal cancer therapy when it comes to increased efficacy and resistance prevention due to these changes [46].

Conclusion

Silver nanoparticles (AgNPs) have exhibited themselves as versatile and effective agents when they are combined in treatment plans in the process of treating cancer. Their exceptional physicochemical properties, such as high surface area, tuneable dimensions, and ease of functionalisation, enable enhanced administration of drugs, immunological modulation, radio sensitization, and photothermal/photodynamic effect, and thus offer synergistic benefits compared to the current monotherapies. Preclinical studies have time and again demonstrated that they are capable of better targeting of the cancerous cells, breaking the resistance to medications, and reducing the possibility of recurrence. Problems related to lack of clearance, off-target toxicity, and unpredictable synthesis protocol still limit clinical translation. To overcome these challenges and ensure safe and effective application, it will be necessary to both use green production methods and alter the surface (making it biocompatible) and accurately adjust the dose. Their full potential as a therapy can also be unlocked by developing personalized nanomedicine, where AgNP-based formulations will be adapted to each patient as well as the unique tumor biology in that patient. Appropriate development and manufacturing of AgNPs can make a big difference to the next era of oncology care because of ongoing improvements in both nanotechnology and in regulation and incorporation into novel modalities, hybrid combinations such as care using artificial intelligence (AI)-based treatment planning.

Ethical Approval

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Competing Interests

No Competing Interests.

Availability of Data and Materials

All data is available in the manuscript file.

Conflict of Interest

No conflict of interest.

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