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A REVIEW ON SILVER NANOPARTICLE FORMULATION OF CISPLATIN FOR LUNG CANCER THERAPY

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Abstract
Lung cancer remains a leading cause of global cancer mortality, and cisplatin continues to serve as a first-line chemotherapeutic agent in its management. However, the clinical utility of cisplatin is limited by poor solubility, dose-limiting toxicities, and the development of drug resistance. Advances in nanotechnology have opened new avenues for drug delivery, with silver nanoparticles (AgNPs) emerging as promising carriers owing to their intrinsic anticancer properties, high surface area, and ease of functionalization. Cisplatin-loaded AgNPs have demonstrated improved pharmacokinetic behavior, sustained release, and selective tumor accumulation, thereby enhancing therapeutic efficacy while reducing systemic toxicity. Preclinical studies have shown significant cytotoxicity against lung cancer cell lines, inhibition of tumor growth in animal models, and reduced nephrotoxicity compared to free cisplatin. The synergistic action of cisplatin-induced DNA cross-linking and AgNP-mediated reactive oxygen species generation further enhances apoptosis and autophagy in resistant cancer cells. Nevertheless, challenges such as nanoparticle stability, potential silver-induced toxicity, scale-up limitations, and regulatory barriers hinder clinical translation. Future perspectives include targeted surface modifications, integration with immunotherapy or radiotherapy, and personalized nanomedicine strategies. Collectively, cisplatin–AgNPs represent a promising therapeutic platform with potential to overcome current limitations of lung cancer chemotherapy.

Keywords: Cisplatin; Silver nanoparticles; Lung cancer; Nanotechnology; Drug delivery; Apoptosis; Reactive oxygen species; Multidrug resistance; Controlled release; Personalized nanomedicine

INTRODUCTION

Lung cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide, accounting for nearly 18% of total cancer deaths annually. Despite advancements in screening and treatment modalities, the prognosis of lung cancer patients continues to be poor, largely due to late diagnosis, rapid disease progression, and limited effectiveness of conventional therapeutic strategies [1, 2]. Chemotherapy continues to be a cornerstone in the management of lung cancer, particularly in advanced stages, where surgical and radiological interventions often provide limited benefits. However, conventional chemotherapy is frequently associated with systemic toxicity, drug resistance, and non-specific biodistribution, which collectively diminish therapeutic efficacy and patient quality of life [3, 4].

Cisplatin, a platinum-based chemotherapeutic agent, has long been employed as a first-line treatment for various solid tumors, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Its mechanism of action involves the formation of platinum–DNA adducts, leading to DNA cross-linking, inhibition of replication, and subsequent induction of apoptosis in rapidly dividing cancer cells. Nevertheless, the clinical utility of cisplatin is considerably limited by several drawbacks. Among these, dose-dependent nephrotoxicity remains the most significant adverse effect, while additional toxicities such as ototoxicity, gastrointestinal disturbances, and neurotoxicity further restrict its safe therapeutic window. Moreover, poor aqueous solubility and the development of intrinsic or acquired drug resistance in tumor cells reduce the long-term effectiveness of cisplatin-based regimens. These challenges highlight the urgent need for improved delivery systems that can enhance cisplatin's therapeutic index while minimizing systemic side effects [5].

In recent decades, nanotechnology has emerged as a transformative platform in drug delivery, offering innovative approaches to overcome the limitations of conventional chemotherapy. Nanoparticle-based carriers are capable of improving drug solubility, prolonging

circulation time, enabling controlled drug release, and facilitating targeted delivery to tumor tissues via the enhanced permeability and retention (EPR) effect. In addition, nanocarriers provide opportunities to co-deliver therapeutic agents and circumvent mechanisms of multidrug resistance, thereby enhancing overall anticancer efficacy. Among the diverse range of nanomaterials investigated for biomedical applications, metallic nanoparticles have gained considerable attention due to their unique physicochemical and biological properties [6, 7].

Silver nanoparticles (AgNPs) have recently emerged as promising candidates in cancer therapy due to their inherent anticancer activity, biocompatibility, and ease of surface modification. Their ability to generate reactive oxygen species (ROS), disrupt mitochondrial function, and induce apoptosis in cancer cells makes them particularly advantageous in combination with conventional chemotherapeutics. The integration of cisplatin with silver nanoparticles offers a dual therapeutic strategy, wherein the cytotoxic potential of cisplatin is synergistically enhanced by the intrinsic anticancer properties of AgNPs. Moreover, the nanoparticle-mediated delivery of cisplatin improves solubility, promotes selective accumulation at the tumor site, and reduces off-target toxicity, addressing major limitations associated with its clinical use. Therefore, the development of cisplatin-loaded silver nanoparticles represents a novel and promising approach for lung cancer therapy, potentially improving treatment outcomes and patient survival rates.

Cisplatin: Mechanism and Limitations

Cisplatin is one of the most widely used platinum-based chemotherapeutic agents and remains a cornerstone in the treatment of various malignancies, including lung cancer. Its antitumor activity is primarily attributed to its ability to interact with nuclear DNA and disrupt essential cellular processes. Once inside the cell, cisplatin undergoes aquation reactions, whereby chloride ligands are replaced with water molecules due to the lower intracellular chloride concentration. This activation step allows cisplatin to form covalent bonds with DNA bases, predominantly at the N7 position of guanine residues. The resulting DNA adducts, including intrastrand and interstrand cross-links, distort the DNA double helix, interfere with replication and transcription, and ultimately trigger DNA damage response pathways. These molecular events activate apoptotic signaling cascades, leading to programmed cell death in rapidly proliferating tumor cells [8-10].

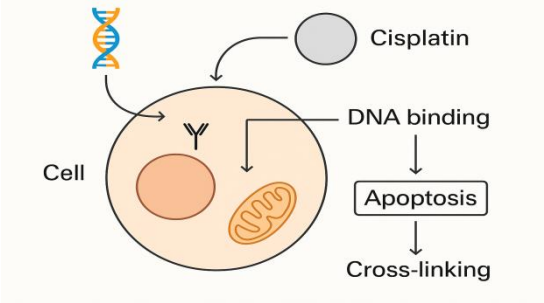


Fig.1. Schematic representation of the mechanism of action of cisplatin in cancer cells.

The pharmacokinetics and biodistribution of cisplatin are critical in determining both its efficacy and toxicity profile. After intravenous administration, cisplatin exhibits rapid systemic distribution and binds extensively to plasma proteins, particularly albumin, thereby influencing its circulation time and bioavailability. The drug is predominantly cleared by renal excretion, with significant accumulation observed in the kidneys, liver, and other highly perfused organs. While this distribution pattern contributes to its antineoplastic activity, it also accounts for dose-limiting organ toxicities. Notably, the short plasma half-life and non-specific tissue uptake reduce the fraction of the drug reaching the tumor site, thereby compromising therapeutic outcomes[11,12].

One of the major limitations of cisplatin therapy is its broad spectrum of toxicities, which often necessitate dose reduction or discontinuation of treatment. Nephrotoxicity is the most severe and well-documented adverse effect, resulting from platinum accumulation in renal tubular epithelial cells and subsequent oxidative stress, inflammation, and apoptosis. In addition, ototoxicity characterized by irreversible hearing loss, and neurotoxicity manifesting as peripheral neuropathy, further impair the patient's quality of life. Other systemic toxicities such as myelosuppression, gastrointestinal disturbances, and electrolyte imbalances further restrict its safe therapeutic window[13].

The long-term clinical application of cisplatin is also hampered by the development of drug resistance, which represents a major obstacle in lung cancer therapy. Cisplatin resistance may arise through multiple mechanisms, including reduced intracellular drug accumulation via altered membrane transporters, increased detoxification by glutathione and metallothioneins, enhanced DNA repair capacity, and inhibition of apoptosis through dysregulation of signaling pathways such as p53, Bcl-2, and PI3K/Akt. These adaptive responses allow tumor cells to evade cisplatin-induced cytotoxicity, leading to therapeutic failure and disease relapse. Moreover, the heterogeneity of lung cancer further complicates resistance mechanisms, necessitating the development of novel delivery systems to restore and enhance cisplatin sensitivity [14, 15].

Collectively, while cisplatin continues to play a pivotal role in lung cancer management, its clinical utility is significantly restricted by unfavorable pharmacokinetics,

dose-limiting toxicities, and the emergence of resistance. These challenges strongly justify the exploration of advanced drug delivery platforms, such as nanoparticle-based formulations, to improve therapeutic efficacy and overcome inherent limitations.

Silver Nanoparticles (AgNPs) in Cancer Therapy

Silver nanoparticles (AgNPs) have gained significant attention in recent years as promising nanomaterials for cancer therapy due to their unique physicochemical and biological properties. Their effectiveness largely depends on factors such as particle size, shape, surface charge, and colloidal stability. Smaller-sized nanoparticles generally exhibit enhanced cellular uptake and increased surface reactivity, enabling better interaction with biomolecules within the tumor microenvironment. The shape of AgNPs—whether spherical, triangular, or rod-like-also influences their biological behavior, with spherical nanoparticles being the most widely studied for drug delivery. Furthermore, the surface charge (zeta potential) governs nanoparticle stability in biological fluids and affects their interaction with cell membranes, where positively charged AgNPs often demonstrate higher cellular internalization. Stability is equally critical, as aggregation of AgNPs can compromise their therapeutic potential and increase nonspecific toxicity. Thus, controlling these physicochemical parameters during synthesis is essential for optimizing their application in cancer treatment [16-19].

The anticancer activity of AgNPs is primarily attributed to their ability to generate reactive oxygen species (ROS), which cause oxidative stress and disrupt redox homeostasis in cancer cells. Elevated ROS levels damage cellular components such as lipids, proteins, and nucleic acids, ultimately triggering mitochondrial dysfunction. This mitochondrial impairment leads to the release of cytochrome c and subsequent activation of caspase-dependent apoptotic pathways. Additionally, AgNPs can induce autophagy and necrosis in certain cancer cells, further contributing to their cytotoxic potential. Importantly, the selective cytotoxicity of AgNPs is believed to arise from their preferential accumulation in tumor cells, which exhibit higher metabolic activity and greater oxidative stress vulnerability compared to normal cells [20].

Several advantages support the utilization of AgNPs in cancer therapy. Their high surface-to-volume ratio enhances drug loading capacity and facilitates efficient interaction with target biomolecules. The ease of surface functionalization allows conjugation with targeting ligands, antibodies, or polymers, thereby improving tumor selectivity and reducing off-target effects. Moreover, AgNPs enable controlled and sustained drug release, minimizing systemic toxicity while maximizing therapeutic outcomes. Their inherent anticancer activity further provides a synergistic effect when combined with chemotherapeutics, offering a dual-action mechanism.

The synthesis of AgNPs can be achieved through both chemical and green synthesis methods. Conventional chemical approaches, including chemical reduction and photochemical methods, allow precise control over nanoparticle size and morphology but often involve toxic reagents that raise concerns regarding biocompatibility. In contrast, green synthesis has emerged as a sustainable alternative, employing plant extracts, microorganisms, or natural polymers as reducing and stabilizing agents. This approach not only minimizes environmental hazards but also imparts additional biological activity from phytochemicals or biomolecules used during synthesis. Green-synthesized AgNPs are particularly attractive for biomedical applications due to their improved safety profile and eco-friendly production [21, 22].

Collectively, AgNPs present themselves as multifunctional platforms in oncology, combining intrinsic cytotoxic properties with the capacity for drug delivery and targeted therapy. Their potential role in enhancing the therapeutic index of conventional drugs, such as cisplatin, underscores their significance in the future of nanomedicine for lung cancer treatment.

Cisplatin-Loaded Silver Nanoparticles

The integration of cisplatin into silver nanoparticle (AgNP) platforms has been extensively investigated to overcome the limitations of conventional cisplatin therapy. Several formulation strategies have been employed for the preparation of cisplatin-loaded AgNPs, with the most common being chemical reduction, green synthesis, and encapsulation methods. In the chemical reduction approach, cisplatin is either co-reduced with silver precursors or adsorbed onto pre-formed AgNPs using reducing agents such as sodium borohydride or hydrazine. Although this method provides precise control over particle morphology, the use of toxic reagents raises biocompatibility concerns. Green synthesis, on the other hand, employs plant extracts, microbial cultures, or biopolymers as reducing and stabilizing agents, offering an eco-friendly and safer alternative for biomedical applications. Encapsulation strategies involve embedding cisplatin within polymeric coatings on AgNP surfaces (such as PEG, chitosan, or dextran), which improve stability and facilitate controlled drug release. Each method presents unique advantages, with the choice of technique largely dictated by the intended therapeutic application and desired physicochemical properties [23, 24].

Optimization of cisplatin–AgNP formulations is crucial to ensure therapeutic efficiency. Particle size plays a pivotal role in determining biodistribution, tumor penetration, and clearance pathways, with nanoparticles in the range of 20–100 nm generally considered optimal for cancer targeting via the enhanced permeability and retention (EPR) effect. Zeta potential is another important factor, as it influences colloidal stability and cellular uptake, with moderately negative or slightly positive surface charges

being preferable for systemic circulation. Loading efficiency, defined as the amount of cisplatin successfully incorporated into the nanoparticles, must be maximized to achieve therapeutic dosing while minimizing drug wastage. Additionally, long-term stability of the cisplatin–AgNP formulation is essential to prevent aggregation and premature drug release, which could compromise efficacy and safety [25,26].

Controlled release kinetics represent a significant advantage of cisplatin-loaded AgNPs. Unlike free cisplatin, which is rapidly cleared from systemic circulation and distributes nonspecifically, AgNPs enable sustained release of the drug over an extended period. This release profile reduces fluctuations in plasma concentration, thereby minimizing peak-related toxicity while maintaining therapeutic levels. The incorporation of surface coatings and functional groups can further modulate release behavior, allowing for stimuli-responsive delivery triggered by pH, redox state, or enzymatic activity within the tumor microenvironment. Such controlled release not only enhances cytotoxicity against tumor cells but also reduces off-target effects on healthy tissues [27].

Comparative studies have consistently demonstrated that cisplatin–AgNP formulations offer several advantages over free cisplatin. Enhanced aqueous solubility and improved tumor selectivity via passive (EPR effect) and active (ligand-mediated) targeting mechanisms lead to greater intracellular accumulation in lung cancer cells. Importantly, the combination of AgNPs' intrinsic pro-apoptotic properties with cisplatin's DNA-damaging effect produces a synergistic anticancer response. Moreover, the use of nanocarrier systems reduces systemic toxicity, particularly nephrotoxicity and ototoxicity, which are major dose-limiting adverse effects of free cisplatin. Collectively, cisplatin-loaded AgNPs represent a promising nano-enabled therapeutic strategy, offering improved pharmacokinetic behavior, enhanced efficacy, and superior safety compared to conventional cisplatin formulations [28].

Mechanism of Action of Cisplatin–AgNPs in Lung Cancer

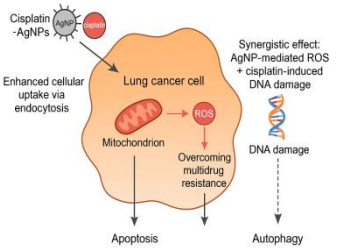
The therapeutic superiority of cisplatin-loaded silver nanoparticles (AgNPs) in lung cancer lies in their ability to exploit multiple complementary mechanisms that collectively enhance antitumor efficacy while reducing systemic toxicity. One of the fundamental advantages is the improved cellular uptake of cisplatin when delivered via AgNPs. Unlike free cisplatin, which enters cells primarily through passive diffusion and is often subjected to efflux by membrane transporters, AgNPs are internalized efficiently through endocytosis. This nanoparticle-mediated uptake results in higher intracellular accumulation of cisplatin, thereby increasing its effective concentration at the site of action within lung cancer cells.

Once internalized, cisplatin–AgNPs exert a synergistic effect by combining the DNA-damaging properties of cisplatin with the intrinsic cytotoxic potential of AgNPs. Cisplatin induces DNA cross-linking and helix distortion, leading to replication arrest and activation of DNA damage response pathways. Simultaneously, AgNPs stimulate the generation of reactive oxygen species (ROS), which induce oxidative stress and mitochondrial dysfunction. The dual insult-cisplatin-mediated genotoxic stress and AgNP-induced oxidative damage-amplifies apoptosis signaling and enhances overall cytotoxicity against lung tumor cells.

Another key mechanism by which cisplatin–AgNPs improve therapeutic outcomes is through the overcoming of multidrug resistance (MDR), a major limitation in conventional chemotherapy. MDR in lung cancer is frequently mediated by efflux pumps such as P-glycoprotein, increased DNA repair capacity, and anti-apoptotic signaling. AgNPs circumvent these mechanisms by disrupting mitochondrial function, impairing ATP production required for efflux activity, and modulating apoptotic regulators. Furthermore, the nanoparticle delivery system shields cisplatin from rapid efflux, ensuring prolonged intracellular retention. This dual approach significantly enhances drug sensitivity in resistant lung cancer cells.

In addition to apoptosis, cisplatin–AgNPs can trigger autophagy pathways, further contributing to tumor suppression. AgNP-induced oxidative stress leads to the activation of autophagic signaling, resulting in the degradation of damaged organelles and proteins. While autophagy may initially serve as a survival mechanism, persistent activation under cisplatin–AgNP treatment drives cancer cells toward programmed cell death. This interplay of apoptosis and autophagy ensures comprehensive elimination of tumor cells, particularly in resistant populations.

Taken together, the mechanism of cisplatin–AgNPs in lung cancer involves enhanced cellular internalization, synergistic cytotoxicity via ROS and DNA damage, reversal of multidrug resistance, and activation of multiple cell death pathways. These combined effects establish cisplatin–AgNPs as a potent therapeutic platform with the potential to surpass the limitations of conventional cisplatin therapy [29,30].



Preclinical Studies

Preclinical evaluations of cisplatin-loaded silver nanoparticles (AgNPs) have demonstrated promising

outcomes in both in vitro and in vivo settings. In vitro cytotoxicity studies on lung cancer cell lines such as A549 and H1299 revealed enhanced apoptotic induction and lower IC_{50} values compared to free cisplatin, confirming superior potency. In vivo studies using murine lung cancer xenograft models further validated these findings, showing significant tumor growth inhibition, delayed progression, and improved survival rates. Comparative analyses highlighted that cisplatin–AgNPs outperform free cisplatin and other nanocarrier systems by providing higher tumor selectivity, enhanced intracellular accumulation, and synergistic anticancer effects. Safety evaluations indicated reduced systemic toxicity, particularly nephrotoxicity and ototoxicity, due to controlled release and targeted biodistribution. Pharmacokinetic investigations showed sustained and controlled drug release profiles, minimizing burst release and maintaining therapeutic concentrations. Biodistribution studies confirmed preferential accumulation in tumor tissues and lungs through the enhanced permeability and retention effect, with reduced deposition in kidneys and liver, thereby effectively lowering off-target toxicity and addressing cisplatin's dose-limiting side effects [31-34].

Challenges and Limitations

Despite the encouraging outcomes demonstrated in preclinical studies, several challenges hinder the clinical translation of cisplatin-loaded silver nanoparticles (AgNPs). One of the major concerns is the stability of AgNPs in biological fluids, as nanoparticles tend to aggregate or undergo surface modifications in the presence of proteins, electrolytes, and other biomolecules, which can significantly alter their pharmacokinetics and therapeutic efficacy. Additionally, while AgNPs possess inherent anticancer activity, their potential toxicity at higher doses remains a pressing issue. Excessive accumulation of silver in non-target organs, such as the liver, spleen, and kidneys, may lead to oxidative stress, inflammation, and cytotoxicity in healthy tissues. Another critical barrier is scale-up and reproducibility, as laboratory synthesis methods often yield heterogeneous particles, and replicating these characteristics consistently at industrial scale poses technical and economic challenges. Moreover, regulatory and clinical translation hurdles further complicate their development, given the lack of standardized guidelines for nanoparticle-based formulations, limited long-term safety data, and the need for comprehensive pharmacological and toxicological profiling before approval for human use.

Future Perspectives

To address these challenges, future research should focus on advanced strategies that enhance both safety and efficacy of cisplatin–AgNP formulations. Surface modification with ligands, antibodies, or peptides represents a promising approach to achieve tumor-specific targeting, thereby improving selectivity and minimizing off-target effects. Combining cisplatin–AgNPs with other treatment modalities, such as immunotherapy or radiotherapy, may provide synergistic therapeutic benefits and overcome resistance mechanisms more effectively. Furthermore, advances in personalized nanomedicine are expected to tailor nanoparticle formulations based on individual patient profiles, tumor genetics, and microenvironmental factors, maximizing treatment efficacy while minimizing toxicity. From a translational perspective, clinical trial considerations must prioritize the evaluation of long-term safety, biodistribution, and dose optimization, alongside comparative studies with existing nanocarrier systems. Establishing standardized regulatory frameworks and scalable, reproducible synthesis protocols will also be essential to bridge the gap between preclinical promise and clinical application.

Conclusion

Cisplatin-loaded silver nanoparticles represent a novel and effective nanotechnology-based approach for lung cancer therapy. By enhancing solubility, stability, and tumor-specific delivery, these formulations significantly improve the therapeutic index of cisplatin while minimizing nephrotoxicity, ototoxicity, and systemic side effects. Preclinical studies have confirmed their superior cytotoxicity, sustained release behavior, and ability to overcome multidrug resistance through synergistic induction of apoptosis and autophagy. Despite these promising outcomes, challenges such as nanoparticle stability in biological fluids, silver-associated toxicity at higher doses, and barriers in large-scale reproducibility remain to be addressed. Furthermore, regulatory frameworks and clinical validations are critical for translation into routine therapy. Future research should focus on surface engineering, ligand-directed targeting, and integration with immuno- and radiotherapy, alongside personalized approaches tailored to patient-specific tumor biology. Collectively, cisplatin–AgNP formulations hold significant promise in redefining lung cancer chemotherapy and bridging the gap between laboratory innovation and clinical application.

Author Contributions

Sohitha Mulupuri: Conceptualization, literature review, drafting of the initial manuscript.

Mounika Vuyyuru: Data collection, critical analysis of preclinical and pharmacokinetic studies, figure preparation. Navya Tokala: Compilation of references, preparation of tables, manuscript editing.Patibandla **Jahnavi:** Supervision, final manuscript revision, and overall guidance.

Conflict of Interest

The authors declare no conflict of interest

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