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RESEARCH PAPER

Synergistic Effects of Silica Nanoparticles with Cisplatin in Ovarian Cancer Management: A Review

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ABSTRACT

Ovarian cancer remains one of the most lethal gynecological malignancies, with high recurrence rates and chemoresistance posing significant clinical challenges. Cisplatin, a cornerstone chemotherapeutic agent, is limited by systemic toxicity, acquired resistance, and poor tumor targeting. Recent advances in nanotechnology offer promising strategies to enhance cisplatin's therapeutic profile, with silica nanoparticles (SiNPs) emerging as a versatile platform for targeted drug delivery. This review explores the synergistic effects of SiNPs and cisplatin in ovarian cancer management, emphasizing their combined potential to overcome conventional treatment barriers. SiNPs' unique properties—including biocompatibility, tunable porosity, and surface functionalization—enable improved cisplatin encapsulation, controlled release, and tumor-specific delivery via enhanced permeability and retention (EPR) effects. Preclinical studies highlight how SiNPs enhance cellular uptake, reduce off-target toxicity, and sensitize resistant ovarian cancer cells to cisplatin by modulating apoptotic pathways and the tumor microenvironment. Furthermore, co-delivery systems incorporating SiNPs and cisplatin demonstrate synergistic suppression of tumor growth in vivo, alongside improved pharmacokinetics. Despite these advances, challenges such as long-term biocompatibility, scalability, and regulatory hurdles remain critical barriers to clinical translation. This review synthesizes current evidence, underscores the mechanisms underlying SiNP-cisplatin synergy, and discusses future directions, including stimuli-responsive nanocarriers and combinatorial approaches with immunotherapy. By addressing these interdisciplinary opportunities, SiNP-cisplatin formulations hold transformative potential for personalized ovarian cancer therapy, offering a blueprint for enhanced efficacy and reduced adverse effects in oncology.

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INTRODUCTION

Ovarian cancer remains one of the most lethal gynecologic malignancies, accounting for approximately 314,000 new cases and 207,000 deaths globally in 2020. Its high mortality is attributed to nonspecific early symptoms, leading to late-stage diagnoses (70% of cases at advanced stages) and rapid metastasis[1]. Current first-line treatments involve cytoreductive surgery followed by platinum-based chemotherapy, such as cisplatin or carboplatin [2]. However, recurrence occurs in 75% of patients, often accompanied by chemoresistance and systemic toxicity, which severely limit therapeutic efficacy and patient survival [3]. Cisplatin, a cornerstone of ovarian cancer chemotherapy, exerts cytotoxic effects by forming DNA crosslinks, triggering apoptosis through DNA damage response pathways [4]. Despite its potency, clinical utility is hampered by two major challenges, Resistance arises via multifactorial mechanisms, including increased efflux by ATP-binding cassette (ABC) transporters (e.g., P-glycoprotein), enhanced DNA repair, and detoxification by glutathione (GSH) [5]. Hypoxia-inducible factor-1 (HIF-1) activation further exacerbates resistance by upregulating multidrug resistance protein 2 (MRP2) and GSH synthesis. Dose-limiting nephrotoxicity, neurotoxicity, and myelosuppression occur due to non-selective biodistribution, necessitating strategies to improve tumor targeting [6]. Nanotechnology has emerged as a transformative approach to overcome these limitations [7]. Silica nanoparticles (SiNPs), particularly mesoporous silica nanoparticles (MSNs), offer unique advantages for drug delivery: SiNPs are chemically inert, with tunable pore sizes (2–50 nm) and surface functionalization capabilities, enabling high drug-loading capacity and controlled release [8]. Their nanoscale size (10–200 nm) promotes passive tumor targeting via leaky tumor vasculature, while surface modifications (e.g., PEGylation) extend circulation time and reduce immune clearance [9]. SiNPs can co-deliver chemotherapeutics, siRNA, or photosensitizers, enabling combination therapies to address resistance mechanisms. For instance, MSNs co-loaded with cisplatin and HIF-1 inhibitors (e.g., acriflavine) demonstrated synergistic antitumor effects by suppressing resistance pathways [10].

The integration of cisplatin with SiNPs addresses both pharmacological and biological challenges, SiNPs enhance cisplatin's tumor accumulation while reducing off-target toxicity [11].

This paper explores the synergy between SiNPs and cisplatin represents a shift in ovarian cancer management, offering solutions to resistance, toxicity, and heterogeneous drug delivery. This review explores the mechanistic insights, preclinical advancements, and translational potential of this combinatorial approach.

SILICA NANOPARTICLES (SINPS): PROPERTIES AND APPLICATIONS

Structural and functional characteristics of SiNPs

Silica nanoparticles (SiNPs) are nanostructured materials composed primarily of silicon dioxide (SiO_2). They exhibit unique physicochemical characteristics that allow for tunability based on synthesis methods, surface modifications, and application requirements [12]. Their structural diversity plays a crucial role in determining their functional properties, which impact performance in biomedical, catalytic, and electronic applications. SiNPs can be classified into different categories based on their architecture and porosity [12]. Mesoporous silica nanoparticles (MSNs) exhibit well-ordered 2D hexagonal or 3D cubic pore structures, pore diameters range between 2–50 nm [13], optimized for biomolecular encapsulation, improving drug-loading efficiency, large pore volumes (>1 cm^3/g) facilitate diffusion and controlled release of payloads, tunable porosity allows selective adsorption of small molecules [14], optimizing carrier properties in drug delivery and sensing applications, frequently synthesized via sol-gel or soft-templating methods. Solid silica nanoparticles (SSNPs) are non-porous, spherical nanoparticles ranging in size from 10–200 nm [15], typically used for imaging applications due to dense silica matrices that provide stability, surface functionalization is crucial for modifying interactions in biomedical systems, often employed in catalysis, biosensing, and contrast-enhanced imaging techniques, exhibits minimal swelling or degradation under physiological conditions, ensuring long-term biocompatibility [16]. Hollow silica nanospheres (HSNs) are characterized by a hollow core surrounded by a mesoporous shell, central cavity allows for the encapsulation of hydrophobic drugs, contrast agents, and functional nanoparticles, shell thickness and porosity can be tailored via synthetic approaches such as template-assisted

sol-gel processing, promotes controlled release and reduced burst effect, enhancing therapeutic efficacy, suitable for applications in targeted drug delivery and imaging diagnostics[17]. SiNPs possess several intrinsic properties that make them highly versatile, chemical inertness and thermal stability ensure their resistance to enzymatic degradation and chemical decomposition under physiological conditions [18], guaranteeing reliability in biomedical and industrial applications, surface chemistry and modifiability through silanol (Si-OH) groups allow covalent bonding with targeting ligands and functional moieties [19], these ligands can include folate, antibodies, or aptamers for cancer targeting, stimuli-responsive polymers such as polyethylene glycol (PEG) or polyacrylic acid enhance stability in biological environments, controlled drug release mechanisms enable responsive drug delivery systems based on external stimuli such as pH, temperature, or enzymatic activity [20], optical properties and imaging compatibility allow modified SiNPs to serve as fluorescent probes, plasmonic nanocarriers, and MRI contrast agents depending on functional coatings and dopant inclusion such as rare-earth elements or transition metals [21]. Due to their versatile nature, SiNPs are widely applied in various fields including biomedical applications for drug delivery, biosensors, theranostics, and regenerative medicine [22], catalysis in heterogeneous catalysts for organic transformations and photocatalytic processes, environmental applications for heavy metal adsorption, gas separation, and water purification, electronic devices in nanoelectronics, semiconductors, and advanced energy storage systems [23].

Advantages of SiNPs in drug delivery

Silica nanoparticles, particularly mesoporous variants, demonstrate physicochemical characteristics that render them applicable for use in controlled drug delivery systems [24]. Compared to conventional nanocarriers such as liposomes and polymeric nanoparticles, silica nanoparticles provide enhanced structural stability, increased surface area, and chemical modifiability [13]. Amorphous silica is classified as generally recognized as safe by the U.S. Food and Drug Administration, indicating minimal systemic cytotoxicity under physiological conditions [25]. The rate of degradation and clearance is influenced by particle size, morphology, and ambient pH. Toxicity profiles are correlated with parameters such as diameter, surface charge, surface silanol density, and administration route [26]. Proper tuning of these parameters allows minimization of adverse biological interactions [27]. Mesoporous silica nanoparticles possess high surface areas exceeding 1,000 square meters per gram and pore volumes greater than 1 cubic centimeter per gram [28]. The pore diameters are tunable within the mesoporous range, which allows encapsulation of a variety of therapeutic agents via adsorption or covalent bonding [29]. Loading capacities for chemotherapeutics such as cisplatin, paclitaxel, and doxorubicin are typically reported in the range of 20 to 30 percent by weight [30]. This is influenced by molecular size, charge interactions, loading technique, and solvent conditions. Encapsulation within the porous matrix mitigates premature degradation and enzymatic inactivation, enhancing plasma stability and reducing nonspecific biodistribution [31]. Surface modification is enabled by the abundance of silanol groups on the silica nanoparticle surface. Functionalization with ligands including folate, HER2 antibodies, and RGD peptides supports receptor-mediated endocytosis [32]. It depends on receptor expression, ligand-receptor affinity, and nanoparticle surface valency. Surface grafting with polyethylene glycol reduces protein corona formation, inhibits recognition by phagocytic cells, and prolongs systemic circulation by minimizing clearance via the reticuloendothelial system [33]. The molecular weight and grafting density of polyethylene glycol affect hydrodynamic diameter and pharmacokinetic behaviour [34]. Coating with pH-sensitive or redox-labile moieties such as chitosan, polydopamine, or disulfide-containing linkers allows drug release in response to acidic pH or elevated glutathione levels typical of tumor microenvironments and intracellular compartments [35]. Silica nanoparticles enable co-delivery of multiple therapeutic agents with differing physicochemical properties [36]. Co-encapsulation of chemotherapeutics with genetic agents such as siRNA or miRNA allows dual action involving apoptosis induction and suppression of resistance pathways [37]. Co-delivery of antioxidants alongside conventional drugs reduces oxidative stress. Nanoparticles can be engineered for sequential drug release through differential pore structures or core–shell designs, where one drug is released rapidly and another is retained for

sustained action [38]. These profiles are governed by diffusion kinetics, nanoparticle degradation, and drug–matrix interactions. Applications of silica nanoparticles extend beyond oncology [39].

Current applications of SiNPs in cancer therapy

In the domain of chemotherapy enhancement, mesoporous silica nanoparticles loaded with cisplatin have been utilized to improve intracellular drug delivery [40]. Some studies involving SKOV3 human ovarian carcinoma cells indicated that cisplatin-loaded MSNs produced a threefold increase in cytotoxicity compared to free cisplatin, which was attributed to elevated endocytotic uptake and increased endo-lysosomal escape, thereby promoting intracellular accumulation and subsequent DNA crosslinking activity [41]. In theranostic applications, silica nanoparticles doped with gadolinium ions have been synthesized to allow for dual functionality in both diagnostic imaging and therapeutic delivery. These particles were functionalized to carry cisplatin while maintaining paramagnetic properties suitable for magnetic resonance imaging (MRI). This allowed for direct correlation of drug delivery efficiency with anatomical localization, contributing to improved assessment of therapeutic outcome and potential dose adjustment [42]. In the context of immunomodulation, porous silica nanoparticles have been developed to co-deliver cisplatin and immune-stimulatory agents such as cytosine-phosphate-guanine (CpG) oligonucleotides [43].

CISPLATIN IN OVARIAN CANCER: CURRENT STATUS AND CHALLENGES

Cisplatin's mechanism of action in targeting cancer cells

Cisplatin, chemically identified as cis-diamminedichloroplatinum(II), is a platinum-based chemotherapeutic agent that mediates cytotoxicity through the induction of extensive DNA damage [44]. The mechanism of action initiates following passive diffusion or active transport via copper transporters such as CTR1 across the plasma membrane of target cells [45]. Once internalized into the cytosol, cisplatin undergoes aquation due to the relatively low intracellular chloride concentration (~4–20 mM), which contrasts with extracellular chloride levels (~100 mM). The replacement of the two chloride ligands with water molecules produces highly electrophilic, mono- and diaquated platinum species [46]. These reactive aquated complexes preferentially coordinate to nucleophilic sites on DNA, with the N7 position of guanine bases being the primary binding site. Cisplatin predominantly forms 1,2-intrastrand crosslinks between adjacent guanine residues (d(GpG)) or between guanine and adenine (d(ApG)), which together account of cisplatin-DNA adducts [47]. Additionally, 1,3-intrastrand and interstrand crosslinks may also occur but to a lesser extent. These covalent adducts induce localized DNA helix bending, resulting in severe structural distortion of the B-DNA conformation [48]. Such alterations impair the progression of DNA and RNA polymerases, leading to stalling of replication forks and inhibition of transcriptional machinery [49]. The recognition of DNA-cisplatin adducts is mediated by several damage response proteins, including high-mobility group box 1 (HMGB1), mismatch repair proteins (e.g., MSH2, MLH1), and nucleotide excision repair complexes [50]. The persistent presence of unrepairable adducts triggers activation of the DNA damage response (DDR) signaling cascade. Sensor kinases such as ataxia-telangiectasia mutated (ATM) and ATM and Rad3-related (ATR) phosphorylate downstream effector proteins including checkpoint kinase 1 (CHK1), checkpoint kinase 2 (CHK2), and tumor suppressor p53 [51]. Phosphorylated p53 accumulates and transactivates pro-apoptotic genes such as BAX, PUMA, and NOXA, while concurrently suppressing anti-apoptotic signals such as BCL-2 and MCL-1 [52]. This culminates in mitochondrial outer membrane permeabilization (MOMP), release of cytochrome c into the cytosol, and activation of the caspase cascade, primarily caspase-9 followed by caspase-3 and caspase-7, resulting in execution-phase apoptosis [53]. In ovarian cancer cells, the high mitotic index enhances the efficacy of cisplatin by increasing the likelihood of DNA damage during S-phase replication, where DNA lesions are most detrimental [54]. However, cisplatin lacks intrinsic tumor specificity and exerts cytotoxic effects on rapidly proliferating non-malignant cells, particularly in the gastrointestinal epithelium, renal proximal tubules, bone marrow, and cochlear hair cells [55]. These off-target effects contribute to a spectrum of dose-limiting toxicities, including nephrotoxicity, myelosuppression, neurotoxicity, and ototoxicity, thereby constraining the maximum tolerated dose and therapeutic window [56]. Moreover, intrinsic

and acquired resistance mechanisms in ovarian cancer, such as enhanced DNA repair capacity (e.g., upregulation of ERCC1), drug efflux via ATP-binding cassette (ABC) transporters, cytoplasmic sequestration by thiol-containing molecules (e.g., glutathione, metallothioneins), and evasion of apoptosis further complicate sustained cisplatin responsiveness [57].

Limitations: Drug resistance, systemic toxicity, and poor bioavailability

Cisplatin, while widely utilized in the treatment of ovarian cancer, is associated with several intrinsic and extrinsic limitations that significantly impair its therapeutic efficacy and clinical utility. These limitations can be broadly categorized into drug resistance, systemic toxicity, and poor bioavailability, all of which contribute to suboptimal treatment outcomes and restrict long-term use in oncologic settings [58]. Drug resistance represents a multifactorial and progressive challenge that compromises cisplatin sensitivity in ovarian cancer cells. One primary mechanism involves diminished intracellular accumulation due to the downregulation or functional inactivation of copper transporter 1 (CTR1), which mediates the active influx of cisplatin across the plasma membrane [59]. In parallel, increased activity of efflux transporters such as ATP-binding cassette (ABC) proteins—including multidrug resistance-associated protein 2 (MRP2) and P-glycoprotein (ABCB1)—further reduces intracellular drug concentration by promoting active excretion of cisplatin or its conjugates [60]. Additionally, elevated levels of intracellular thiol-containing biomolecules, particularly glutathione (GSH) and metallothioneins [61], facilitate the detoxification of cisplatin through covalent conjugation, resulting in the formation of non-reactive platinum–sulfur complexes that are subsequently exported or sequestered [62].

DNA repair capacity plays a pivotal role in mediating acquired resistance to cisplatin-induced genotoxic stress. The nucleotide excision repair (NER) pathway, notably through the upregulation of excision repair cross-complementation group 1 (ERCC1), effectively recognizes and excises cisplatin-DNA adducts, thereby allowing restoration of DNA integrity [63]. Moreover, restoration or overexpression of homologous recombination (HR) components, such as BRCA1 and BRCA2 proteins, enables high-fidelity repair of DNA double-strand breaks that arise secondary to replication fork collapse at cisplatin-induced lesions [64]. Tumor microenvironmental factors further exacerbate resistance, particularly under hypoxic conditions, which induce the stabilization and activation of hypoxia-inducible factor 1-alpha (HIF-1α). HIF-1α modulates the expression of genes associated with drug efflux and metabolic reprogramming, including ABC transporters and enzymes involved in redox homeostasis, thereby enhancing the adaptive resistance phenotype of cancer cells [65].

Systemic toxicity constitutes a major barrier to the prolonged and repeated administration of cisplatin. The preferential accumulation of cisplatin in renal proximal tubular epithelial cells results in dose-dependent nephrotoxicity, characterized by elevated serum creatinine, reduced glomerular filtration rate, and histopathological evidence of tubular necrosis [66]. The underlying mechanisms involve the generation of mitochondrial reactive oxygen species (ROS), activation of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), and depletion of intracellular antioxidants [67]. Additionally, cisplatin induces peripheral neurotoxicity, manifesting as sensory neuropathy due to axonal degeneration and mitochondrial impairment within dorsal root ganglion neurons [68]. Ototoxicity, another dose-limiting effect, is attributed to cisplatin-induced apoptosis of cochlear outer hair cells and spiral ganglion neurons, often resulting in irreversible sensorineural hearing loss [69]. These toxicities collectively limit the maximum cumulative dose of cisplatin that can be safely administered. Poor bioavailability further compromises the clinical performance of cisplatin. Following systemic administration, cisplatin undergoes rapid distribution and elimination, with renal excretion accounting for a significant proportion of drug clearance [70]. The administered dose remains bioavailable to target tumor tissues due to rapid binding to plasma proteins, nonspecific tissue uptake, and glomerular filtration [71]. This pharmacokinetic profile necessitates high initial dosing to achieve therapeutic concentrations at the tumor site, which concurrently amplifies the risk of systemic adverse effects and contributes to a narrow therapeutic index. Furthermore, the absence of tumor-specific accumulation exacerbates off-target toxicity and undermines treatment specificity [56].

Strategies to overcome cisplatin's drawbacks

Multiple strategic interventions are under investigation to address the pharmacological limitations associated with cisplatin therapy in ovarian cancer, with particular emphasis on improving therapeutic efficacy, reducing systemic toxicity, and overcoming acquired drug resistance. These strategies primarily encompass nanotechnology-based delivery systems, combinatory pharmacologic approaches, stimuli-responsive drug release mechanisms, and toxicity-attenuating platforms[72]. The integration of these modalities into cisplatin-based treatment regimens is supported by mechanistic rationale and corroborated by emerging preclinical data [73]. Nanotechnology-driven delivery systems, especially mesoporous silica nanoparticles (MSNs), represent a robust platform for the encapsulation and controlled release of cisplatin [74]. The high surface area, tunable pore size), and large pore volume of MSNs allow for high loading efficiencies and stabilization of the cisplatin payload [75]. Encapsulation within the silica matrix physically isolates cisplatin from the extracellular biological environment, thereby limiting premature aquation and detoxification by extracellular thiol-rich biomolecules such as glutathione (GSH) and albumin [76]. Moreover, MSNs passively accumulate in tumor tissues via the enhanced permeability and retention (EPR) effect due to the leaky vasculature and impaired lymphatic drainage characteristic of solid tumors [77]. Functionalization of MSNs with tumor-targeting ligands—such as folic acid, epidermal growth factor receptor (EGFR) antibodies, or RGD peptides—further enhances selective uptake via receptor-mediated endocytosis in ovarian cancer cells overexpressing these molecular markers, thereby improving intratumoral accumulation and reducing off-target cytotoxicity to non-malignant tissues [77]. Combination therapies leveraging cisplatin and molecular adjuvants aim to exploit synthetic lethality and mitigate resistance pathways. Co-administration of cisplatin with poly(ADP-ribose) polymerase (PARP) inhibitors, such as olaparib, is particularly efficacious in BRCA1/2-mutated ovarian cancers, which exhibit homologous recombination deficiency (HRD) [78]. Inhibition of PARP enzymes impairs single-strand break repair, which, when combined with cisplatin-induced DNA crosslinks and double-strand breaks, results in cumulative genotoxic stress and apoptosis [79]. Cisplatin's integration with immunotherapeutic agents, particularly immune checkpoint inhibitors such as anti-programmed death-1 (PD-1) monoclonal antibodies, enhances immunogenic cell death (ICD) [80].

Stimuli-responsive delivery systems improve spatial and temporal control over cisplatin release, limiting systemic exposure and enhancing localized activity within the tumor microenvironment (TME) [81]. Mesoporous SiNPs engineered with acid-labile linkers, such as hydrazone or acetal bonds, facilitate pH-triggered drug release in acidic tumor interstitium (pH ~6.5) or lysosomal compartments (pH ~5.0). Similarly, incorporation of disulfide linkages between cisplatin and the SiNP surface or gatekeeper molecules enables GSH-mediated cleavage and intracellular release in cancer cells characterized by elevated cytoplasmic GSH levels (>10 mM) [82]. These stimuli-responsive strategies ensure that cisplatin is preferentially liberated at the disease site, thereby maximizing local efficacy and minimizing systemic toxicity. Efforts to mitigate cisplatin-induced organ toxicities focus on modulating its biodistribution through nanoparticle surface modification [83]. PEGylated SiNPs reduce renal uptake by increasing hydrodynamic diameter and conferring steric hindrance, which diminishes filtration through glomerular membranes and minimizes accumulation in proximal tubular cells [84].

SYNERGISTIC EFFECTS OF SINPS AND CISPLATIN

Mechanisms of synergy: Enhanced drug delivery, reduced toxicity, and overcoming resistance

The synergistic interaction between silica nanoparticles and cisplatin in the context of ovarian cancer therapy is characterized by the convergence of complementary physicochemical, pharmacokinetic, and pharmacodynamic mechanisms that collectively enhance drug delivery efficiency, attenuate systemic toxicity, and counteract multiple pathways of cisplatin resistance [85]. The structural and functional versatility of mesoporous silica nanoparticles (MSNs) provides a multifunctional platform capable of modulating the spatial and temporal distribution of cisplatin, thereby optimizing its therapeutic index [86]. The enhancement of drug delivery by SiNPs is attributed to their intrinsic properties including high specific surface area, tunable pore diameters, and high pore volume, which enable encapsulation of cisplatin [56]. The chemical confinement

of cisplatin within the mesoporous matrix delays aquation and minimizes degradation by extracellular thiols [75]. Additionally, MSNs can be engineered for sustained or stimuli-triggered drug release. pH-sensitive coatings such as chitosan, poly(L-histidine), or polyacrylic acid respond to the mildly acidic tumor microenvironment, releasing encapsulated cisplatin over 24–48 hours in tumor interstitium, release at physiological pH (7.4) [87]. This site-selective release minimizes premature systemic exposure and increases the intratumoral drug concentration [88]. The systemic toxicity profile of cisplatin is substantially mitigated through SiNP encapsulation. The silica matrix prevents non-specific interactions with renal tubular epithelium and neuronal tissues, while surface PEGylation imparts hydrophilicity and steric hindrance, reducing recognition by the mononuclear phagocyte system (MPS) and subsequent hepatic and splenic uptake. Pharmacokinetic analyses in rodent models have demonstrated reduction in renal platinum accumulation and preservation of glomerular filtration rate and serum creatinine levels when cisplatin is administered in PEG-SiNP form[84]. Additionally, the modulation of the nanoparticle surface with zwitterionic or hydrophilic polymers improves hemocompatibility and minimizes protein corona formation. SiNPs also facilitate the circumvention of several mechanisms of cisplatin resistance [89]. Intracellular detoxification via glutathione is addressed by co-encapsulation of cisplatin and buthionine sulfoximine (BSO), a γ-glutamylcysteine synthetase inhibitor that suppresses GSH synthesis. This co-delivery results in significant depletion of intracellular GSH levels and restoration of cisplatin-DNA adduct formation in resistant A2780cis cell lines [90]. SiNPs can also be conjugated with targeting moieties such as folate, transferrin, or antibodies to exploit overexpressed surface receptors on ovarian cancer cells and mediate receptor-ligand internalization [91]. This targeted internalization pathway bypasses classical drug efflux pumps such as P-glycoprotein (P-gp/ABCB1) and multidrug resistance-associated proteins (MRPs), which are often upregulated in chemoresistant phenotypes [92]. Moreover, co-delivery of cisplatin and poly(ADP-ribose) polymerase (PARP) inhibitors such as olaparib in a single SiNP construct enables synergistic DNA damage induction in BRCA-mutant cells [93]. Cisplatin causes DNA crosslinks and double-strand breaks, while olaparib prevents the repair of single-strand breaks via inhibition of base excision repair [94]. In homologous recombination-deficient cancer cells, this dual insult induces synthetic lethality, resulting in irreversible genomic instability and apoptosis [95].

Role of SiNPs in improving cisplatin pharmacokinetics and tumor targeting

Silica nanoparticles improve the pharmacokinetic parameters and tumor-targeting capacity of cisplatin through a series of physicochemical modifications that influence biodistribution, circulation time, and tumor localization [96]. Unmodified cisplatin displays rapid renal clearance, poor tumor accumulation, and a short plasma half-life, which limits its therapeutic window and necessitates high dosing [97]. Encapsulation of cisplatin in PEGylated mesoporous silica nanoparticles modifies these pharmacokinetic characteristics. Surface PEGylation using linear or branched polyethylene glycol increases the hydrodynamic diameter and imparts steric stabilization, reducing opsonization by plasma proteins and minimizing clearance by the mononuclear phagocyte system [98]. Tumor targeting is improved through both passive and active mechanisms. Passive targeting is mediated by the enhanced permeability and retention (EPR) effect, which is dependent on nanoparticle size, surface charge, and shape [99]. SiNPs exhibit preferential accumulation in tumor tissues with leaky vasculature. In peritoneal ovarian cancer xenografts, negatively charged SiNPs, synthesized through silanization with carboxyl-terminated ligands such as 3-(trihydroxysilyl) propyl methylphosphonate or succinic anhydride, have shown to reduce lymphatic uptake and drainage [100]. This charge-dependent trafficking increases tumor retention compared to positively charged analogs, which are more rapidly cleared via lymphatics. Active targeting is achieved through ligand-mediated receptor recognition [101]. HER2-targeted SiNPs are synthesized by covalent attachment of trastuzumab or HER2-binding peptides to the SiNP surface via EDC/NHS chemistry. HER2 is overexpressed in a subset of ovarian cancer cells including SKOV3 [102].

PRECLINICAL AND CLINICAL STUDIES

Laiba Saeed et al [103] examined how silica nanoparticles, quercetin, and cisplatin affect

ovarian cancer. Cisplatin is effective but has high toxicity, while quercetin has strong anti-cancer properties. 40 female albino rats were divided into eight groups for testing. Various treatments were applied, including a control group and groups treated with quercetin, silica nanoparticles, cisplatin, or combinations thereof. The results showed that the control group with tumors had increased body weight and altered hormone levels, but the group treated with quercetin-cisplatin-silica nanoparticles showed significant improvement.

Xiaojuan Zhang et al [104] developed a one-pot synthesis approach for a microporous organosilica shell-covered cisplatin nanoplatform the usage of a reverse microemulsion method, and explored its software in co-delivering acriflavine (ACF) for inhibiting hypoxia-inducible component-1 (HIF-1). The resulting nanoparticles were tunable, and they could be optimized to a monodisperse population of particles within the preferred size variety (40-50 nm). further, organic mPEG2000-silane and tetrasulfide bond-bridged organosilica have been integrated into the surface and silica matrix of nanoparticles for extended blood circulation and tumor-selective glutathione-responsive degradation, respectively. After reaching the tumor sites, cisplatin caused cancer cellular demise and activated HIF-1 pathways, resulting in obtained drug resistance and tumor metastasis. To address this problem, ACF turned into co-loaded with cisplatin to prevent the formation of HIF-1α/β dimers and suppress HIF-1 function. subsequently, the efficacy of cisplatin was improved, and cancer metastasis changed into inhibited. Both in vitro and in vivo consequences counseled that this core-shell nanostructured cisplatin transport gadget represented a relatively efficacious and promising nanoplatform for the synergistic delivery of combination therapies related to cisplatin.

CONCLUSION AND FUTURE PERSPECTIVES

Ovarian cancer continues to pose major treatment challenges due to cisplatin resistance, toxicity, and limited bioavailability. Silica nanoparticles (SiNPs) offer a promising platform to enhance cisplatin delivery by improving tumor targeting, reducing off-target effects, and overcoming resistance mechanisms. Preclinical data show improved drug uptake and efficacy with SiNP-cisplatin systems. However, issues like long-term safety, manufacturing scale-up, and regulatory uncertainty hinder clinical progress. Despite these limitations, SiNP-cisplatin formulations represent a step toward more precise, effective cancer treatment.

Development of hybrid SiNPs may combine drug delivery with additional therapeutic functions. Machine learning may help optimize synthesis parameters for better drug loading and release. Long-term safety studies are needed to understand degradation and accumulation. Scalable and cost-effective synthesis methods are required to support clinical translation. Co-delivery of cisplatin with other therapies may improve treatment response. Functionalization with biomarkers may allow real-time monitoring and dose adjustment. Standardized regulatory guidelines are necessary for evaluation and approval. Clinical trials should target specific ovarian cancer subtypes. Cost-reduction strategies are important to improve global accessibility.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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