Gold Nanoparticle-Based Drug Delivery Systems for Reducing Chemotherapy Side Effects: A Systematic Review

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ABSTRACT

Background: Cancer remains a leading global health burden, with nearly 20 million new cases recorded in 2022. Chemotherapy, while central to treatment, is limited by systemic toxicity, poor tumor selectivity, and multidrug resistance, compromising both survival and quality of life. **Objective:** This systematic review evaluates the extent to which gold nanoparticle-based drug delivery systems (AuNP-DDS) reduce chemotherapy-associated side effects while enhancing tumor-selective delivery, by examining their underlying mechanisms, preclinical and clinical efficacy, and safety profiles. **Methods:** A systematic literature search was conducted following PRISMA 2020 guidelines across PubMed, Scopus, ScienceDirect, and Google Scholar for articles published between 2020 and 2025. Ten studies comprising clinical trials, in vitro, and in vivo models met eligibility criteria and were qualitatively synthesized. **Results:** Across the included evidence, AuNP-DDS consistently demonstrated reduced systemic toxicity and enhanced tumor-selective accumulation through combined passive (EPR-driven) and active (ligand-based) targeting. Benefits were documented for doxorubicin, gemcitabine, cisplatin, and siRNA-based constructs. No dose-limiting toxicities emerged from reviewed clinical studies, and stimuli-responsive formulations further curtailed off-target drug exposure. **Conclusion:** AuNP-DDS demonstrate considerable promise for limiting chemotherapy-induced harm through targeted delivery and controlled drug release. However, additional clinical validation and standardized production methods remain essential before widespread clinical adoption.

Keywords: AuNPs; cancer therapy; chemotherapy side effects; enhanced permeability and retention; gold nanoparticles; targeted drug delivery.

Introduction

Cancer has remained one of the defining health challenges of the twenty-first century. According to GLOBOCAN 2022 data, the disease was responsible for nearly 10 million deaths in 2020, and by 2022 the number of new diagnoses had climbed to approximately 20 million.[1] Rather than a single condition, cancer encompasses more than 100 distinct histological subtypes, with lung, breast, colorectal, prostate, and hepatocellular malignancies contributing the greatest share of both incidence and mortality worldwide. Despite advances in molecular oncology, imaging technology, and targeted biological therapies, cancer remains the second leading cause of death globally, underscoring the urgent need for safer and more effective treatments.[1–3]

For many patients, particularly those with advanced or metastatic disease, chemotherapy remains the standard systemic treatment. However, its fundamental limitation persists: most chemotherapeutic drugs are poorly equipped to distinguish malignant cells from healthy, rapidly dividing tissues such as bone marrow, intestinal epithelium, and hair follicles.[4] This lack of selectivity produces a predictable constellation of complications, including myelosuppression, peripheral neuropathy, cardiotoxicity, nephrotoxicity, alopecia, and severe gastrointestinal disturbances that frequently necessitate dose reduction or treatment cessation. The cumulative cardiotoxicity of doxorubicin and the nephrotoxicity of cisplatin exemplify dose ceilings imposed by safety concerns rather than efficacy.[4]

Nanotechnology has emerged as a promising solution, offering novel approaches to refine anticancer drug delivery. By engineering carriers at the nanoscale (approximately 1–100 nm), researchers gain unprecedented control over physicochemical behavior that traditional formulations cannot replicate.[5] Among various nanocarrier candidates, gold nanoparticles (AuNPs) have attracted sustained attention due to their chemical stability, low intrinsic toxicity, minimal immunogenicity, and surface chemistry amenable to drug conjugation, ligand attachment, and PEGylation. Their optical properties, particularly surface plasmon resonance, enable photothermal therapy alongside conventional drug delivery.[6]

Two complementary mechanisms explain AuNP-based tumor targeting. Passive targeting relies on the enhanced permeability and retention (EPR) effect: structurally abnormal tumor vasculature with fenestrations spanning 200–800 nm, combined with impaired lymphatic drainage, facilitates nanoparticle accumulation within the tumor microenvironment.[7] Active targeting builds upon this by attaching tumor-specific recognition molecules antibodies, aptamers, folic acid, or peptides to AuNP surfaces,

promoting receptor-mediated endocytosis with greater specificity. When both mechanisms act synergistically, systemic drug circulation decreases, thereby mitigating chemotherapy-associated side effects.[8]

Stimuli-responsive platforms further enhance safety by releasing payloads only upon exposure to tumor-specific conditions, including acidic pH (5.0–6.5), elevated intracellular glutathione (GSH), increased matrix metalloproteinase activity, or externally applied near-infrared light.[9] This conditional release mechanism offers an additional safeguard for healthy tissues, directly addressing one of the most persistent drawbacks of conventional chemotherapy.

Despite encouraging preclinical findings, the path to routine clinical adoption remains incomplete. Manufacturing at scale, long-term biodistribution, chronic toxicity, and regulatory approval remain unresolved challenges.[10] With these considerations in mind, this systematic review examines existing evidence on AuNP-based drug delivery systems covering applications, mechanisms, therapeutic efficacy, and safety in reducing chemotherapy-induced side effects from literature published between 2020 and 2025.

Methods

This review adopted a systematic method for evaluating published evidence on gold nanoparticle-based drug delivery systems aimed at reducing chemotherapy-related side effects, following the PRISMA 2020 framework across the stages of identification, screening, eligibility assessment, and final inclusion.

Search Strategy

The literature search covered four databases: PubMed (MEDLINE), Scopus, ScienceDirect, and Google Scholar. Conducted in June 2025, the search combined Medical Subject Headings (MeSH) with relevant free-text terms joined by Boolean operators: ("gold nanoparticles" OR "AuNPs" OR "GNPs") AND ("cancer" OR "tumor" OR "neoplasm") AND ("drug delivery" OR "chemotherapy" OR "drug carrier" OR "nanocarrier") AND ("side effects" OR "toxicity" OR "adverse effects" OR "safety"). Eligibility was restricted to English-language articles published from January 2020 through May 2025.

PICO Framework

Population: individuals diagnosed with cancer as well as experimental cancer models, encompassing both in vitro and in vivo studies. Intervention: gold nanoparticle-based drug delivery systems (AuNP-DDS) used to deliver chemotherapeutic agents in a targeted manner. Comparison: standard chemotherapy or free, unencapsulated chemotherapeutic drugs. Outcome: reduction in chemotherapy-related toxicity, greater

therapeutic effectiveness, and an improved overall safety profile.

Inclusion and Exclusion Criteria

Eligible studies needed to be original research articles, systematic reviews, or clinical trials published in peer-reviewed journals; written in English; centered on gold nanoparticle (AuNP)-based drug delivery systems used in cancer chemotherapy; published between 2020 and 2025, with a single exception made for a Phase 0 clinical trial from 2021 retained because of its clinical relevance; and required to present quantitative findings related either to therapeutic efficacy or toxicity.

Excluded from the review were case reports, editorials, conference proceedings, and letters to the editor; studies concerned only with the synthesis or characterization of AuNPs without any therapeutic application; investigations limiting AuNP use strictly to diagnostic or imaging purposes with no therapeutic component; papers lacking adequate methodological detail or extractable quantitative data; and any duplicate publications or studies drawing on overlapping datasets.

PRISMA Flowchart

Database searching identified a total of 147 records, distributed across PubMed (n = 42), Scopus (n = 38), ScienceDirect (n = 35), and Google Scholar (n = 32), with no duplicates detected. Screening of titles and abstracts led to the exclusion of 107 records that did not satisfy the predefined inclusion criteria. The remaining 40 articles proceeded to full- text review, after which 30 were removed due to irrelevant interventions or outcomes, including work centered on photothermal or photodynamic therapy without a drug delivery component, non-gold nanoparticle systems, nanoparticle synthesis studies lacking therapeutic testing, and conventional chemotherapy research with no gold nanoparticle involvement. This process left 10 studies that met every eligibility requirement and were carried forward into the qualitative synthesis. Figure 1 presents the complete study selection process in PRISMA flow-diagram format.

Data Extraction

Variables extracted included the author(s) and year of publication, study design, sample characteristics, intervention type, outcome measures, and principal findings. Both reviewers cross-checked the extracted data independently to minimize errors and bias. Where discrepancies arose during study selection or data extraction, these were settled through discussion until agreement was reached; unresolved disagreements were referred to a third reviewer for a final decision.

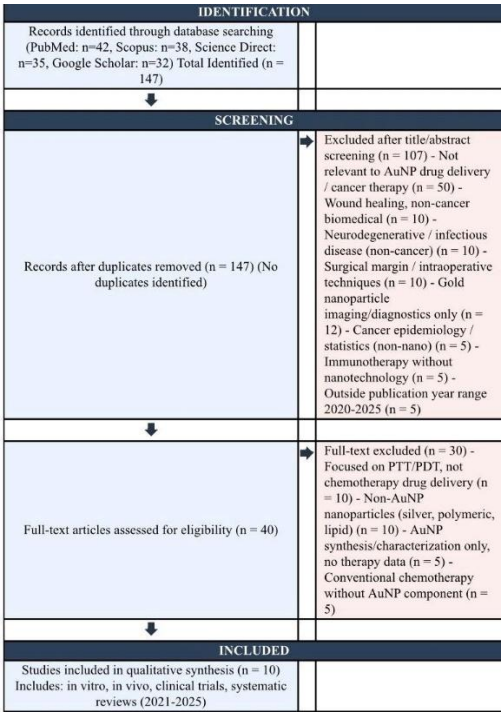

Figure 1. PRISMA flowchart of the systematic literature search and selection process

Results

Ten studies met the eligibility requirements and were incorporated into this qualitative synthesis, representing a mix of study designs that included in vitro experiments, in vivo animal models, computational (in silico) analyses, systematic reviews, and a single human clinical trial. The research originated from a range of countries, among them the United States, Iran, South Korea, China, Canada, and Brazil, reflecting growing international engagement with AuNP-based nanomedicine. Cancer types under investigation included breast cancer, glioblastoma, pancreatic cancer, colorectal cancer, and other malignancies, with therapeutic payloads spanning doxorubicin, gemcitabine, siRNA constructs, and cisplatin derivatives. Table 1 summarizes the characteristics and principal findings of the ten included studies.

Table 1. Data Extraction Table / Characteristics of Included Studies

No	Author/Year	Title	Study Design	Sample	Intervention	Main Finding
1	Abdollahzade et al., 2023	Targeted delivery of doxorubicin and FOXM1 aptamer using AuNPs modified with AS1411 and ATP aptamers	In vitro & In vivo	4T1 & MCF-7 cells; BALB/c mice bearing 4T1 tumor	AuNPs-AFPA-Dox: aptamer-functionalized AuNPs co-delivering Dox + FOXM1 aptamer	Significant tumor growth inhibition vs. free Dox; reduced toxicity to non-target cells; enhanced targeting via nucleolin receptor overexpression
2	Zhang et al., 2023	Clinical translation of gold nanoparticles for drug delivery and therapeutic applications	Clinical Review (>20 trials analyzed)	Human subjects in Phase I/II clinical trials	GNPs as drug delivery vehicles, photothermal therapy agents, and intrinsic therapeutic platforms	No major safety concerns; CYT-6091 (AuNP-rhTNF) demonstrated tumor-selective accumulation and improved safety profile vs. free rhTNF

3	Yao et al., 2023	Applications and safety of gold nanoparticles as therapeutic devices in clinical trials	Systematic Review	>20 clinical trials, human subjects	GNPs implemented across multiple delivery routes (IV, intratumoral, topical); various payloads	GNPs demonstrated lower toxicity and favorable side-effect profiles vs. conventional chemotherapy; tumor-targeting via EPR and active mechanisms
4	Elechalawar et al., 2024	Biodistribution and therapeutic efficacy of AuNP-based targeted drug delivery against pancreatic cancer	In vivo	Orthotopic co-implantation pancreatic cancer model (mice)	AuNPs conjugated with cetuximab (C225) + gemcitabine targeting both PCCs and PSCs	Effective tumor growth inhibition in orthotopic model; dual targeting of cancer cells and stellate cells; reduced systemic gemcitabine toxicity

5	Zhang et al., 2025	Cell membrane-coated AuNP-based drug delivery for enhanced antitumor therapy in breast cancer	In vitro & In vivo	MCF-7 cells; xenograft mouse model	M@DOX@AuNPs: DOX loaded onto AuNPs via electrostatic adsorption, coated with cancer cell membrane	Favorable physical stability; time-dependent drug release; reduced off-target toxicity confirmed by histopathology and blood biochemical analysis; enhanced tumor accumulation
6	Alalmaie et al., 2025	Integrating computational insights in AuNP-mediated drug delivery: enhancing efficacy and precision	Computational/In silico study	Molecular dynamics and quantum mechanics simulations	AuNPs functionalized with drug-binding peptides for doxorubicin delivery; size and shape optimization	AuNP size and shape significantly affect drug binding affinity and release kinetics; peptide functionalization enhances targeted delivery precision and reduces off-target binding

7	Kumthekar et al., 2021	First-in-human Phase 0 clinical study of RNA interference-based spherical nucleic acids (AuNP-siRNA) in recurrent glioblastoma	Phase 0 Clinical Trial	8 patients with recurrent glioblastoma multiforme	Spherical nucleic acids: AuNPs conjugated with siRNA targeting Bcl2L12, administered systemically	Blood-brain barrier penetration demonstrated; reduced target gene expression in tumor biopsies; well-tolerated with no dose-limiting toxicities reported
8	Guo et al., 2024	Core-shell microspheres with encapsulated AuNP carriers for controlled release of anti-cancer drugs	In vitro	MCF-7 and PANC-1 cell lines	DOX-loaded AuNPs encapsulated in biodegradable PLGA core-shell microspheres (DOX@Au@MS	Sustained drug release profile; reduced burst release compared to conventional DDSs; cell viability reduced to <20% at therapeutic concentrations; biocompatible scaffold

9	Kesharwani et al., 2023	Gold nanoparticles and gold nanorods in the landscape of cancer therapy	Systematic Review	Multiple preclinical and clinical studies analyzed	AuNPs and AuNRs as carriers for doxorubicin, cisplatin, paclitaxel; surface functionalized with PEG, folate, HER2 antibodies, aptamers	Consistent tumor-selective cytotoxicity; reduced healthy-cell toxicity vs. free drugs; PEGylation extends circulation time and reduces MPS clearance; folate-targeting increases cancer-cell specificity

10	Kaid et al., 2025	Gold nanoparticles: synthesis, properties, shapes, cellular uptake, targeting, release mechanisms and applications in drug delivery	Comprehensive Review	Multiple preclinical in vitro/in vivo models	AuNPs of various morphologies (spheres, rods, stars, cages) loaded with multiple chemotherapeutic agents	Shape-dependent cellular uptake and drug release; rod-shaped AuNPs show superior tissue penetration; stimuli-responsive (pH, GSH, light) release mechanisms significantly reduce off-target drug exposure and systemic side effects

AuNP Formulation Types and Surface Functionalization

The ten included studies demonstrated considerable versatility in AuNP scaffold design. Several distinct functionalization approaches appeared repeatedly:

a. Dual-aptamer conjugation for combined active targeting and gene-level intervention.[11]
b. Cancer cell membrane coating for immune evasion and homotypic tumor recognition.[12]
c. Antibody conjugation (e.g., cetuximab/C225) for receptor-specific targeting in pancreatic cancer.[13]
d. PEGylation to prolong circulation and reduce reticuloendothelial system clearance.[9]
e. Spherical nucleic acid (SNA) architecture for siRNA delivery across the blood-brain barrier.[14]

Safety and Toxicity Profile

The safety findings point in a broadly favorable direction for AuNP-based platforms. Organic-coated and biomimetic formulations cell membrane-coated AuNPs[12] and PLGA-encapsulated microspheres[16] consistently demonstrated good biocompatibility, supported by histopathological and blood biochemistry data showing minimal non-target organ damage. Clinical-stage formulations reported no major safety concerns across more than 20 trials.[15],[17] The Phase 0 study by Kumthekar et al. (2021) found no dose-limiting toxicities even with systemic administration of AuNP-siRNA constructs in glioblastoma patients.[14]

However, formulations built around inorganic, uncoated, or bare AuNP cores require closer scrutiny. Although gold itself is largely inert, gradual accumulation in the liver, spleen, and kidneys over extended periods remains a concern that included studies most tracking animals for relatively short periods were not designed to fully address. Computational analysis indicated that surface functionalization, particularly with targeting peptides, can reduce nonspecific protein adsorption and may lessen unwanted immune activation.[6] On balance, surface-functionalized and biomimetic AuNP formulations offer a more favorable near-term safety profile, whereas bare AuNPs still require longer-term biodistribution and chronic toxicity data before their safety can be firmly established.

Discussion

The EPR Effect and Its Clinical Translational Implications

Passive tumor targeting within AuNP-based drug delivery systems relies heavily on the EPR effect. Tumor blood vessels feature fenestrations spanning 200–800 nm,

considerably wider than gaps in normal vasculature (<8 nm), facilitating nanoparticle extravasation.[7] However, the EPR effect does not behave identically in humans as in mice. Clinical evidence reveals considerable variability in nanoparticle accumulation not only between patients but also across tumor types and individual lesions within the same patient with only approximately 0.7% of an administered nanoparticle dose reaching the tumor site on average.[8]

Despite this constraint, both Yao et al. (2023) and Zhang et al. (2023) reported that AuNP-DDS formulations, including CYT-6091, still achieved sufficient tumor accumulation for clinical benefit, enabling higher therapeutic doses without compromising safety.[15],[17] This finding suggests that the clinical advantage of AuNP-DDS arises not from the EPR effect in isolation but from the interplay of selective accumulation, lower systemic exposure, and controlled release acting synergistically.[7]

Particle Size as a Critical Determinant

Particle size is a decisive factor in translating the EPR effect into meaningful tumor accumulation. AuNPs sized between 20 and 100 nm generally achieve the optimal balance among prolonged circulation, efficient tumor penetration, and adequate cellular uptake. Particles below 10–20 nm undergo rapid renal clearance, whereas particles exceeding 150–200 nm show reduced tumor penetration and increased susceptibility to mononuclear phagocyte system uptake, redirecting them toward the liver and spleen.[7] Thus, size selection shapes biodistribution, therapeutic efficacy, and toxicity as substantially as the EPR effect itself.

Active Targeting: Enhancing Selectivity Beyond Passive Accumulation

Functionalizing AuNP surfaces with targeting ligands pushes tumor selectivity beyond passive accumulation. Abdollahzade et al. (2023) developed a dual-aptamer construct (AS1411 targeting nucleolin + FOXM1 for gene-level intervention), achieving selective cellular uptake while simultaneously influencing oncogenic signaling pathways.[11] Elechalawar et al. (2024) demonstrated that anti-EGFR antibody-functionalized AuNPs effectively homed to tumors overexpressing EGFR.[13] Zhang et al. (2025) employed cancer cell membrane coating to promote immune evasion and homotypic tumor recognition.[12] This biomimetic strategy is particularly noteworthy as it may circumvent the trade-off associated with PEGylation (which extends circulation but can dampen cellular uptake), positioning membrane coating as a promising direction for clinical development.

Clinical Translation: Progress and Remaining Challenges

The Phase 0 trial by Kumthekar et al. (2021) represents a genuine milestone, demonstrating that AuNP-siRNA spherical nucleic acids can cross the blood-brain barrier, silence tumor-related gene expression, and do so without dose-limiting toxicity in glioblastoma patients.[14] For brain tumors, where the blood-brain barrier routinely obstructs conventional chemotherapeutics, this finding carries considerable weight.

Nevertheless, the path to clinical translation is not fully resolved. Manufacturing AuNPs at GMP scale while maintaining consistency in particle size, surface chemistry, and drug loading remains technically demanding and costly.[5] Long-term biodistribution and chronic toxicity particularly liver and spleen accumulation still require rigorous, longer-duration clinical follow-up.

Stimuli-Responsive Systems: Maximizing Therapeutic Index

Stimuli-responsive AuNP platforms add a further layer of safety by concentrating drug release within the tumor microenvironment. pH-responsive designs exploit the acidic tumor environment (pH 5.0–6.5), while glutathione-responsive systems utilize elevated intracellular GSH to trigger payload release.[9]

Guo et al. (2024) demonstrated that PLGA-encapsulated AuNPs produce sustained release profiles, smoothing peak plasma concentrations typical of conventional chemotherapy.[16] Such pharmacokinetic modulation carries real clinical significance, potentially limiting concentration-dependent toxicities such as doxorubicin-related cardiotoxicity and cisplatin-related nephrotoxicity.

Computational Optimization for Rational Design

Computational modeling provides a faster and less costly means of refining AuNP formulations before experimental investment. Alalmaie et al. (2025) demonstrated through molecular dynamics simulations that nanoparticle size and shape substantially influence doxorubicin binding and release kinetics.[6] Peptide functionalization further improved targeting precision while lowering nonspecific protein adsorption, restricting both off-target accumulation and unwanted immune recognition.

Study Limitations and Research Gaps

Several limitations must be acknowledged. Most included studies relied on cancer cell lines or murine xenograft models, which only partially capture human tumor complexity. The EPR effect tends to appear more pronounced and predictable in animal models than in clinical settings. Only one study Kumthekar et al. (2021) with eight patients involved human participants, limiting the generalizability of clinical conclusions.[14]

Considerable variation in AuNP formulation, cancer models, therapeutic payloads, and outcome measures prevented meaningful quantitative meta-analysis. Comparing findings across studies was further complicated by these methodological differences. Future research should prioritize standardized protocols for nanoparticle characterization and outcome reporting.

Future Directions

Continued progress in AuNP-based drug delivery systems depends on developing more advanced strategies: combining AuNP-DDS with cancer immunotherapy to strengthen anti-tumor immune responses, leveraging theranostic applications (integrating imaging and therapy), and utilizing artificial intelligence and machine learning to predict optimal nanoparticle designs and individualize treatment based on tumor biomarkers and vascular characteristics.[6]

Conclusion

This systematic review demonstrates that gold nanoparticle-based drug delivery systems (AuNP-DDS) represent a promising strategy for reducing chemotherapy-related side effects while improving tumor-selective drug delivery. Across the ten included studies covering in vitro, in vivo, computational, and clinical evidence AuNP-DDS consistently demonstrated enhanced tumor selectivity, lower systemic toxicity, and superior safety compared to conventional free chemotherapeutic agents. These advantages arise from the combined effects of passive targeting (EPR effect), active targeting (surface ligands such as aptamers, antibodies, and cell membrane coatings), and stimuli-responsive drug release triggered by tumor-specific conditions, thereby minimizing damage to healthy tissues and reducing toxicities including cardiotoxicity, nephrotoxicity, myelosuppression, and peripheral neuropathy. Clinical findings, particularly the Phase 0 trial of AuNP-siRNA therapy in glioblastoma, further support the translational potential of AuNP-DDS by demonstrating blood-brain barrier penetration, effective gene silencing, and a favorable safety profile. Nevertheless, larger clinical trials, standardized manufacturing protocols, comprehensive long-term safety evaluations, and continued development through immunotherapy integration and AI-assisted nanoparticle design remain essential before these systems can be widely implemented in routine clinical practice. Overall, the available evidence indicates that AuNP-DDS provide a strong foundation for developing safer and more effective cancer therapies in the future.

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