OCTAHEDRON
Drug Research
Vol. 7
Review Article

Gold nanoparticles in drug delivery systems for cancer treatment: A review

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ARTICLE INFO

Article history :
Received 1 May 2025
Received in revised form
14 June 2025
Accepted 15 June 2025
Available online 15 June 2025

Keywords: Gold nanoparticles; Drug delivery; Targeted therapy; Controlled release; Cancer treatment.

ABSTRACT

Gold nanoparticles (AuNPs) have emerged as a promising nanocarrier in cancer therapy due to their unique physicochemical properties, including high stability, biocompatibility, and surface tunability. This review explores the synthesis and functionalization of AuNPs. In addition, the roles of AuNPs in drug delivery systems, highlighting their advantages over conventional cancer treatments, such as improved targeting, enhanced drug bioavailability, and reduced systemic toxicity, are deliberated. Moreover, the mechanisms of AuNP-based drug delivery include passive targeting via the enhanced permeability and retention (EPR) effect and active targeting using functionalized ligands are illustrated. Stimuli-responsive drug release strategies are also discussed, including pH, temperature, and light-triggered mechanisms. This review underscores the transformative potential of AuNPs in treating different cancer types while emphasizing the need for further research to optimize their clinical applicability. Furthermore, their toxicity, biocompatibility, and safe dosage limits are highlighted. Finally, clinical trials and regulatory considerations of the FDA and EMA are mentioned.

1. Introduction

1.1. Overview of cancer treatment challenges

Targeted cancer therapies selectively attack tumor cells by inhibiting key molecules like RTKs, reducing damage to healthy tissues compared to chemotherapy. Initially, single-target drugs like Trastuzumab and Imatinib showed promise, but resistance emerged. Now, the focus is shifting to multi-target inhibitors like Sorafenib and Sunitinib, which block multiple pathways, offering a more effective approach to cancer treatment [1]. Drug resistance is a major cause of cancer treatment failure, closely linked to tumor heterogeneity and the diversity of cancer cell populations within a tumor. This heterogeneity leads to metastatic clones and drug-resistant variants, making treatment more challenging. Recent research highlights the clonal organization of tumors as a key factor in resistance. Understanding the number of tumor subpopulations is crucial, as multiple clones impact therapy effectiveness and

Doi: 10.21608/odr.2025.380813.1053

normal tissue tolerance. The review explores laboratory and clinical strategies to overcome this complex resistance issue [2]. The limited penetration of anticancer drugs through tumor tissue may be an important cause of clinical resistance of solid tumors to chemotherapy [3]. While cancer treatment is improving, chemotherapy-induced toxicities remain a major challenge, leading to severe side effects such as neurotoxicity, hepatotoxicity, nephrotoxicity, and cardiotoxicity. Various strategies are being developed to manage these toxicities, including new diagnostic techniques and treatment regimens. Additionally, cancer therapy imposes a financial burden on patients, including medical costs and indirect expenses like travel and job disruptions. This section explores cancer treatment-related toxicities, their diagnosis, interventions, and clinical strategies for better management [4]. Nanocarriers enhance chemotherapy by improving drug pharmacokinetics and biodistribution. Several nanocarrier-based drugs are in clinical trials or already approved. Future strategies focus on modifying delivery systems and co-encapsulating drugs to overcome drug resistance and improve chemotherapy effectiveness [5]. The blood-brain barrier is a major obstacle to delivering drugs for brain tumor treatment. Future advancements in technology and clinical trials are key to improving drug penetration. Finding a safe and effective way to bypass the BBB could revolutionize brain tumor therapy [6]. The high cost of medications is a major global health challenge, especially in low- and middle-income countries, where drug prices far exceed income levels. Addressing this issue requires regional strategies, multi-stakeholder collaboration, and cost-effectiveness analyses to improve access and affordability [7].

The role of nanotechnology in cancer therapy

Cancer nanotechnology is a rapidly growing field combining science, engineering, and medicine to enhance cancer treatment. It offers innovative solutions for early diagnosis, targeted drug therapy, prevention, and personalized medicine. The focus is on target-specific treatments and early disease detection, making nanotechnology a crucial tool in cancer therapy [8]. Traditional cancer diagnosis methods like surgery, magnetic resonance imaging, and positron emission tomography are costly. Nanoparticles, with their high surface area, targeting abilities, and bioavailability, offer a promising alternative for diagnosis and treatment. Due to their intrinsic anticancer properties, various types—metallic, polymeric, liposomes, quantum dots, and carbon-based nanoparticles—are used for targeted drug delivery and tumor inhibition [9].

1.2.1. Types of Smart Nanoparticles Used in Cancer Therapy

Polymeric nanoparticles revolutionize drug delivery with controlled release, stability, and targeting. They combine organic and inorganic materials to enhance circulation, solubility, and therapeutic effects. Smart nanoparticles can serve both treatment and imaging, while polyethylene glycol conjugates improve drug lifespan and efficiency. Dendrimers are highly branched nanoparticles that improve drug solubility, targeting, and controlled release. They help deliver water-insoluble drugs, cross the blood-brain barrier, and reduce toxicity, making them ideal for cancer therapy. Polymer micelles enhance drug solubility, stability, and targeted delivery while reducing toxicity. They respond to pH changes for controlled release, making them ideal for cancer therapy and ocular drug delivery. Liposomes improve drug delivery by fusing with cell membranes and carrying water- and lipid-soluble drugs. PEGylation enhances stability and circulation time, while smart liposomes enable targeted therapy via pH, enzymes, or light. They are also used for tumor imaging, gene editing, and cancer treatment. Protein nanoparticles enhance drug delivery with high biocompatibility, biodegradability, and targeting ability. Albumin-based carriers improve cancer therapy, as seen in FDA-approved Abraxane for metastatic breast cancer. Cell membrane-coated nanoparticles mimic natural cells to enhance drug delivery, immune evasion, and tumor targeting. Platelet-coated versions with doxorubicin show high anticancer efficacy. Inorganic smart nanocarriers include mesoporous silica nanoparticles (MSNs), which offer high drug loading, biocompatibility, and targeted release. PEGylation improves circulation, while smart MSNs respond to pH, temperature, and enzymes for precise cancer therapy. Moreover, gold nanoparticles (AuNPs) have high stability, biocompatibility, and tunability, making them ideal for cancer diagnosis and therapy. Their near-infrared absorption enables photothermal therapy, imaging, and biosensing. For targeted delivery, auNPs can be functionalized with drugs, peptides, and genes. Their large surface area allows for multimodal cancer treatments, enhancing precision medicine.

Why gold nanoparticles? Unique properties and advantages

Gold nanoparticles exhibit several characteristics that make them ideal for cancer therapy:

1. Size and Shape Versatility: Gold nanoparticles are promising for transfecting target cells with small interfering RNA (siRNA), but their size and shape impact cell uptake. In glioblastoma cells, 50 nm spheres and 40 nm stars had higher uptake and escaped endosomes faster than 13 nm spheres, making them more effective siRNA carriers [10].

Doi: 10.21608/odr.2025.380813.1053

2. Surface Functionalization: Gold nanoparticles are advancing as anticancer agents, with clinical trials underway for photoablation, imaging, radio-sensitization, and drug delivery. Their success depends on precise surface modifications to enhance efficacy and minimize toxicity [11].
3. Biocompatibility and Low Toxicity: Biocompatibility is crucial for inorganic nanoparticles in drug delivery. Stabilized gold nanoparticles (GKNPs) showed high biocompatibility and low toxicity, while GEM-loaded GKNPs enhanced cancer cell inhibition by increasing reactive oxygen species (ROS). GKNPs hold promise as safe and effective drug carriers [12]. Nanotechnology is transforming disease diagnosis, monitoring, and treatment, with AuNPs standing out due to their tunable size, biocompatibility, and functionalization ability. Their optical, electrical, and surface properties make them ideal for biosensing, molecular imaging, and drug delivery, driving innovation in biomedicine [13]. Additionally, AuNPs offer a promising targeted therapy for cancer, reducing chemotherapy side effects. They serve as drug carriers, theranostic agents, and photothermal therapy tools while aiding in bioimaging (MRI, radiotherapy, photo-acoustics). In vitro, studies show anticancer effects, but in vivo, studies highlight the importance of size, dose, and administration route in determining toxicity and bioaccumulation [14]. Moreover, Gold nanostructures (nanorods, nanocages, nanoshells) have tunable optical properties for cancer therapy, diagnosis, and drug delivery. Stimuli-assisted drug delivery systems, especially light-responsive drug delivery systems, offer precise, controlled drug release. Near-infrared drug delivery systems use photothermal effects and up-converting nanoparticles to enhance treatment while minimizing complications [15]. Furthermore, Multidrug resistance (MDR) limits chemotherapy success. A gold nanoparticle drug delivery system (DOX-Hyd@AuNPs) improves doxorubicin uptake and controlled release in acidic organelles, enhancing drug accumulation, retention, and cytotoxicity in MDR cancer cells. This system serves a dual role in overcoming MDR and tracking drug release [16]. In addition, long-circulating AuNPs face challenges in elimination and organ accumulation. Gold-loaded polymeric micelles with smaller AuNPs (0.9 nm vs. 5 nm) improve gold excretion, showing higher clearance from the liver and spleen and increased urinary and fecal elimination. This approach enhances the biodegradability of inorganic nanomaterials, improving their clinical translation [17].

Physicochemical Properties of Gold Nanoparticles (AuNPs) Size, shape, and surface chemistry

2.1.1. Size of Gold Nanoparticles and Its Impact on Biological Behavior

Their size strongly influences auNPs' cellular absorption, biodistribution, Clearance, and overall therapeutic efficacy. Gold nanoparticles may be produced in a range of sizes, from 1 nm to 100 nm, and each size exhibits distinct interactions with biological systems [18]. Small AuNPs (1–10 nm): They are helpful for intracellular medication transport and gene delivery because they can access the nucleus and easily pass through cell membranes. On the other hand, their renal excretion rates are greater [19]. Medium-sized AuNPs (10–50 nm) Exhibit the highest cellular uptake due to optimal interactions with endocytic pathways, making them ideal for targeted drug delivery [19]. Larger AuNPs (50–100 nm) Tend to accumulate more in tumor tissues due to the enhanced permeability and retention effect. However, their uptake by individual cancer cells is lower compared to smaller particles [20]. Regarding the Clearance of gold nanoparticles, the kidneys typically clear AuNPs smaller than 5 nm [21]. Larger AuNPs (above 50 nm) tend to accumulate in the liver and spleen due to uptake by the reticuloendothelial system (RES), impacting their circulation time [22]. Optimized size (10–30 nm) balances circulation time, tumor accumulation, and cellular uptake [23].

2.1.2. Shape of Gold Nanoparticles and Its Influence on Biomedical Applications

There are several ways to create gold nanoparticles, such as spheres, rods, cags, stars, and triangles, and each one has its distinct biological characteristics and optical behaviors, as depicted in Figure 1 [24]. Spherical gold nanoparticles are the most widely utilized form because of their adjustable surface changes, excellent stability, and simplicity of synthesis [18]. They are suitable for drug delivery, imaging, and photothermal therapy. Gold Nanorods (AuNRs) are perfect for photothermal treatment due to their anisotropic optical characteristics, which absorb light in the near-infrared spectrum [25]. They exhibit higher cellular uptake than spherical AuNPs of the same size. [26]. Gold nanocages and hollow nanoparticles are good drug carriers with stimuli-responsive release capabilities due to their large surface area-to-volume ratio [27]. They are used in controlled drug delivery and imaging applications. Gold nanostars and nanotriangles provide strong plasmonic effects and can be used in photothermal therapy, biosensing,

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and imaging [28]. Nanostars support enhanced surface functionalization for targeted cancer therapy.

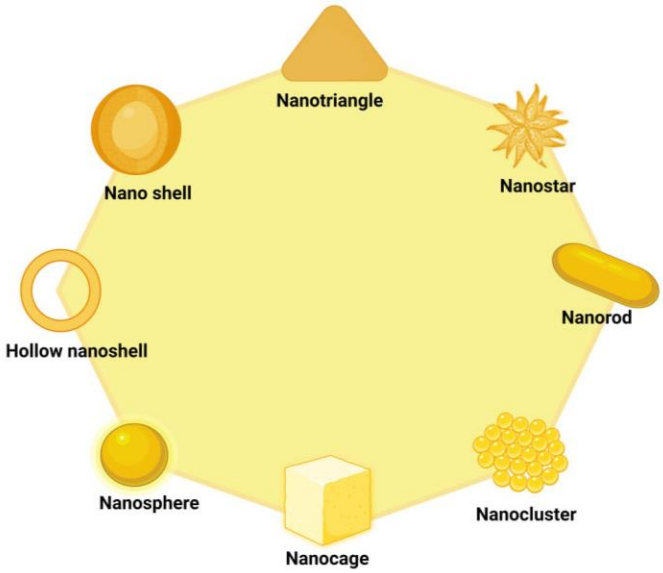

Figure 1: Shapes of AuNPs

2.1.3. Surface Chemistry and Functionalization of Gold Nanoparticles

Their surface chemistry significantly influences the stability, biological interactions, and therapeutic uses of AuNPs. Although gold nanoparticles are naturally inert, they can have different molecules functionalized on their surface to improve target selectivity and biocompatibility, as depicted in Figure 2 [29]. Surface functionalization for stability and biocompatibility includes polyethylene glycol coating, which increases circulation time by preventing protein adsorption and immune recognition [22], enhances biocompatibility, and reduces Clearance by the mononuclear phagocyte system (MPS). Polymers (e.g., chitosan, dextran, PLGA) improve stability in biological fluids and enable controlled drug release [30]. Targeting ligands for selective drug delivery compromises folic acid, which targets folate receptors overexpressed in cancer cells [23]. Peptides and antibodies enhance active targeting and cellular internalization [31]. Stimuli-responsive modifications include pH-responsive coatings, which enable drug release in acidic tumor environments [23]. Light-triggered release mechanisms are used in photothermal therapy (PTT) and photoacoustic imaging [24].

Biocompatibility and stability

2.2.1. Biocompatibility of Gold Nanoparticles

Biocompatibility is a biomaterial's ability to function safely in medical therapy, avoiding harmful effects while promoting optimal cellular or tissue response for effective clinical performance [32]. The most commonly used cell lines to assess biocompatibility are HFB4 normal fibroblast cells and Wi38 human fibroblast cells (38, 39). In the case of AuNPs, their biocompatibility is influenced by size, shape, surface chemistry, and dose. Table 1 illustrates the factors affecting the biocompatibility and stability of gold nanoparticles. Regarding size and biocompatibility, small AuNPs (<5 nm) may penetrate cell membranes and organelles, leading to potential cytotoxic effects due to reactive oxygen species (ROS) generation [33]. Medium-sized AuNPs (10–50 nm) generally show good biocompatibility and are efficiently taken up by cancer cells via endocytosis, making them ideal for drug delivery [19]. Larger AuNPs (>50 nm) tend to accumulate in the liver and spleen, leading to prolonged circulation but possible immune system activation [22]. Concerning shape and biocompatibility, spherical AuNPs are used due to their low toxicity and stable cellular interactions [18]. Gold nanorods exhibit higher cytotoxicity due to their sharp edges and anisotropic shape, which can cause mechanical stress on cell membranes [26]. Gold nanostars can induce higher immune responses than spherical particles but offer strong optical properties for therapy [23]. PEGylation (Polyethylene Glycol Coating) enhances stability and reduces protein adsorption, minimizing immune recognition and prolonging circulation. [22]. Polysaccharide Coatings (Dextran, Chitosan) improve biodegradability and reduce toxicity [30]. In addition, cationic AuNPs (positively charged) Tend to interact more with cell membranes but can induce cytotoxic effects by disrupting lipid bilayers [34]. Moreover, anionic AuNPs (negatively charged) Generally show lower toxicity and better biocompatibility [35]. Interestingly, AuNPs adsorb proteins from plasma as they enter the circulation, creating a protein corona that affects the particles' biological destiny. This impact may change targeted efficiency and improve biocompatibility [36].

2.2.2. Stability of Gold Nanoparticles

Stability is essential for AuNPs to maintain their structure, surface functioning, and therapeutic qualities during drug administration and circulation. When used to treat cancer, unstable nanoparticles may combine, break down, or lose their ability to target. [23]. Factors affecting stability include colloidal stability as surface functionalization with PEG or surfactants prevents aggregation by introducing steric or electrostatic repulsion [22]. Regarding pH and ionic strength sensitivity, AuNPs may aggregate in high-salt environments (such as blood plasma) unless properly coated [37]. pH-sensitive coatings allow controlled drug release in the acidic tumor microenvironment [23]. Moreover, AuNPs are generally inert, but surface modifications (e.g., thiol-based

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linkers) can degrade over time, affecting stability [24].In addition, AuNPs stored in aqueous solutions require stabilizing agents (e.g., citrate, PVP, or PEG) to prevent aggregation and precipitation [35].

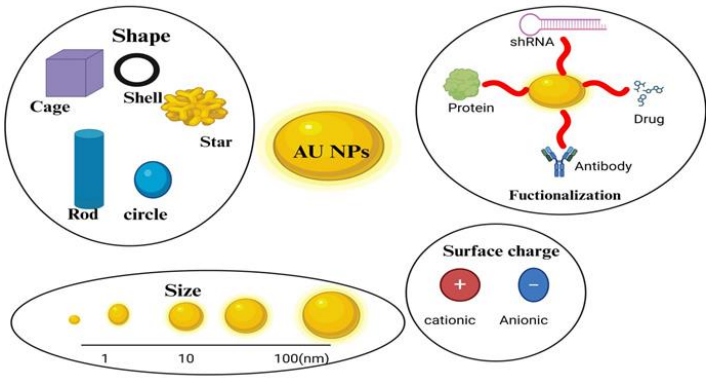

Figure 2. Shape, size, surface charge, functionalization of AuNPs

2.2.3. Toxicity considerations and Clearance of gold nanoparticles

While AuNPs are generally considered biocompatible, their toxicity depends on dose, size, surface charge, and exposure time [38]. Low concentrations (<10 μg/mL) typically show no significant toxicity [39]. High concentrations (>50 μg/mL) may induce oxidative stress, mitochondrial damage, and inflammation [39], as illustrated in Figure 3.

Synthesis and Functionalization of Gold Nanoparticles

Chemical Synthesis

1. Turkevich Method: Uses sodium citrate as a reducing and stabilizing agent, producing spherical AuNPs of 10–100 nm [40].
2. Brust-Schiffrin Method: Employs thiol ligands and organic solvents, yielding monodisperse, stable nanoparticles [41].
3. Seed-Mediated Growth: Uses pre-formed small AuNPs as nucleation centers for controlled growth, enabling the synthesis of non-spherical nanoparticles such as nanorods and nanostars [42].

Advantages:

1. High control over nanoparticle size and shape.
2. Scalable and suitable for large-scale production.

Limitations:

1. Potential toxicity due to residual chemical reagents.

Requires additional purification steps for biomedical applications [43].

Biological Synthesis

1. Microorganisms: Bacteria (*Pseudomonas aeruginosa*) and fungi (*Aspergillus niger*) can reduce gold salts into AuNPs through enzymatic processes [44].
2. Plant-Based Synthesis: Extracts from *Azadirachta indica* (Neem) and *Ocimum sanctum* (Tulsi) serve as natural reducing and stabilizing agents [45].
3. Algae-Based Synthesis: Algae, a varied collection of photosynthetic organisms inhabiting aquatic ecosystems, have attracted considerable interest in recent years as potential biological agents for the environmentally sustainable synthesis of different nanoparticles. This emerging study area is utilizing the distinctive characteristics of algae to enable the synthesis of metal nanoparticles. Scientists are investigating how different reaction circumstances, including pH, temperature, and stirring rate, affect the features of the resultant nanoparticles, such as size, shape, stability, and other relevant qualities. A compelling area of investigation entails utilizing algae to facilitate the production of gold nanoparticles. This research has revealed intriguing insights into the interaction between algae and gold ions during nanoparticle synthesis. In a significant study, Chlorella vulgaris biomass was utilized to convert gold (III) ions to gold (I) ions from a gold chloride solution, as confirmed by X-ray absorption spectroscopy (XAS) data. This study demonstrated the coordination of Au (I) ions with sulfur atoms, perhaps derived from free sulfhydryl residues or lighter atoms, potentially nitrogen [46].

Advantages:

Figure 3. Potential toxic effects of AuNPs

1. Environmentally sustainable with no need for toxic chemicals.
2. It produces biocompatible AuNPs that are ideal for drug delivery.

Limitations:

1. Slower reaction rates compared to chemical synthesis.

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2. Variability in nanoparticle size and shape due to biological diversity [47].

Physical Synthesis

1. Laser Ablation: A high-energy laser beam vaporizes a gold target in liquid, leading to nanoparticle formation [48].
2. Ball Milling: Mechanical grinding of bulk gold into nanoscale particles, sometimes requiring stabilizers to prevent aggregation [49].

Advantages:

1. Produces pure AuNPs without chemical contaminants.
2. It avoids the use of toxic solvents.

Limitations:

1. High energy consumption makes it costly.
2. Difficulty in achieving uniform nanoparticle sizes [50].

Surface modifications and conjugation strategies

Surface Modifications of Gold Nanoparticles

Surface modifications involve coating or functionalizing AuNPs with biomolecules, polymers, or ligands to enhance their properties for drug delivery. Polymers improve the stability, circulation time, and biocompatibility of AuNPs: Polyethylene glycol (PEGylation) reduces immunogenicity and renal Clearance, prolonging circulation time [23] and prevents aggregation by creating a hydrophilic barrier around AuNPs [51]. Chitosan coating enhances muco-adhesion for drug delivery to mucosal tissues [52]. Moreover, it increases cellular uptake due to its positive charge, interacting with negatively charged cell membranes [53]. Polylactic-co-glycolic acid (PLGA) provides controlled drug release, improving therapeutic efficiency [54]. Lipid and protein coatings help in biofunctionalization and cell membrane penetration—lipid bilayers (liposome-coated AuNPs) mimic cell membranes, enhancing cellular uptake [55]. Albumin-functionalized AuNPs improve biocompatibility and prevent non-specific protein adsorption [56].

Conjugation Strategies for Targeted Drug Delivery

Conjugation refers to attaching targeting molecules to AuNPs, allowing them to recognize and bind to specific cancer cells. Covalent conjugation uses thiol (-SH) and amine (-NH_2) functional groups to form strong gold-thiol or gold-amine bonds, ensuring stable drug attachment [43]. Non-covalent conjugation relies on electrostatic interactions, hydrophobic forces, and van der Waals interactions for reversible binding [57].

Mechanisms of Drug Delivery Using AuNPs

Passive Targeting Strategy

The physiological and anatomical distinctions between tumor and normal tissues are the foundation of passive targeting. The main process is the Enhanced Permeability and Retention effect, in which the accumulation of nanoparticles in the tumor microenvironment is caused by leaky tumor vasculature and inadequate lymphatic outflow. Several factors play a role in the efficiency of passive targeting:

1. Nanoparticle Size:

Research indicates that AuNPs with a diameter of 10 to 200 nm effectively accumulate in tumors because they may enter the vasculature without being eliminated by the kidneys [58].

2. Surface Charge and Hydrophobicity: While the immune system quickly eliminates highly charged particles, neutral or slightly negatively charged nanoparticles have longer circulation durations [59].
3. Long Circulation Half-life:
4. Surface alterations such as polyethylene glycol coating, or PEGylation, aid AuNPs in avoiding immune detection, extending their stability and promoting tumor accumulation [60]. Passive targeting offers several advantages, such as utilizing natural tumor physiology for drug accumulation without requiring additional modifications. However, it has notable limitations, including non-specific accumulation in some organs and variation in the EPR effect among different tumors. While it is a simpler and cost-effective approach, it does not ensure high cellular uptake, leading to suboptimal therapeutic effects. Example: Through the EPR effect, PEGylated gold nanoparticles (~100 nm) have been demonstrated to aggregate in lung and breast cancers, increasing the effectiveness of chemotherapy [61].

Active Targeting Strategy

Active targeting is a technique that involves functionalizing AuNPs with specific targeting ligands (such as aptamers, peptides, antibodies, and folic acid) that recognize and bind to overexpressed receptors on cancer cells. This enhances tumor selectivity and cellular internalization, enhancing therapeutic outcomes.

Types of Active Targeting:

1. Receptor-Mediated Targeting: Functionalizing AuNPs with ligands such as trastuzumab (HER2-targeted antibody) allows them to selectively bind to HER2-positive breast cancer cells, significantly improving drug uptake [62].

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2. Stimuli-Responsive Targeting: Some AuNPs are designed to release their drug payload in response to environmental changes (e.g., low pH in tumors), ensuring more localized drug release [63].
3. Magnetic or Light-Triggered Targeting: Gold nanorods can be activated using near-infrared light, which induces localized heat generation (photothermal therapy) and enhances drug delivery effectiveness [64].

With its high tumor selectivity and improved cellular absorption, active targeting is a successful precision medicine strategy. It may, however, cause immunological reactions, necessitate intricate functionalization procedures, and increase production costs. Notwithstanding these difficulties, active targeting minimizes toxicity while boosting therapeutic efficacy by drastically reducing off-target pharmacological effects. For instance, doxorubicin has been effectively delivered to ovarian cancer cells with folic acid-functionalized AuNPs, greatly lowering toxicity in healthy tissues [65].

Table 2 compares between passive and active targeting.

Enhanced permeability and retention (EPR) effect

Mechanism of the EPR Effect

Rapid and unchecked angiogenesis causes tumors to establ -ish an aberrant vasculature, which results in leaky blood vessels with wide endothelial gaps (100–800 nm). In contrast to normal tissues, where endothelial gaps are significantly smaller, tumor tissues have an uneven vascular pattern that makes it possible for nanoparticles, such as AuNPs, to enter and accumulate [58]. Furthermore, tumors' inadequate lymphatic drainage system hinders the quick removal of nanoparticles.

Because of this retention effect, AuNPs can stay in the tumo r microenvironment for longer, improving therapeutic effectiveness and drug bioavailability.

Key Factors Influencing the EPR Effect

1. Nanoparticle Size: AuNPs between 10–200 nm exhibit optimal accumulation due to their ability to leak into tumors but avoid rapid Clearance by the kidneys [59].
2. Surface Modification: PEGylation (polyethylene glycol coating) prevents immune recognition, prolongs nanoparticle circulation and improves EPR-mediated accumulation [66].
3. Tumor Type and Microenvironment: The extent of the EPR effect varies among different tumor types, with some tumors exhibiting higher vascular permeability than others [60].

Limitations and Challenges of the EPR Effect

Despite its advantages, the EPR effect is not universally efficient across all tumors due to several limitations:

1. Tumor Heterogeneity: Not all tumors exhibit the same degree of vascular permeability, affecting nanoparticle penetration [30].
2. High Interstitial Fluid Pressure (IFP): Some tumors develop high internal pressure, which can hinder nanoparticle accumulation [67].
3. Rapid Clearance by the Mononuclear Phagocyte System (MPS): AuNPs without surface modifications may be cleared before reaching the tumor site, reducing their therapeutic impact.

Example 1: Tumors such as pancreatic cancer have a dense stromal barrier that limits the efficiency of the EPR effect, requiring additional targeting strategies to enhance drug delivery [68].

Example 2: Folic acid-functionalized AuNPs have been designed to enhance tumor penetration, bypassing some limitations of the EPR effect [61].

Stimuli-responsive drug release (pH, temperature, light, etc.)

Stimuli-responsive drug release is a very sophisticated method for treating cancer using gold nanoparticles (AuNPs), which allows for precise and regulated drug delivery. This method increases treatment efficacy while lowering systemic toxicity by using environmental (temperature, light, magnetic fields) and internal (pH, enzymes, redox potential) cues to initiate medication release precisely at the tumor site. Gold nanoparticles can be engineered to release therapeutic agents in response to specific tumor-associated conditions:

A. Internal Stimuli (Tumor Microenvironment-Sensitive)

I. pH-Responsive Drug Release: Tumor tissues often exhibit a lower pH (~6.5–6.8) compared to normal tissues (~7.4) due to increased glycolysis and lactic acid production [69].

II. pH-sensitive AuNPs are functionalized with acid-labile linkers (e.g., hydrazone, acetal) that break down under acidic conditions, releasing the drug selectively in the tumor environment [70]. Example: Doxorubicin-loaded AuNPs with pH-sensitive polymer coatings have shown effective tumor-targeted drug release in breast cancer models.

III. Redox-Responsive Drug Release

Tumor cells exhibit high levels of glutathione (GSH), which can break disulfide bonds in AuNP-based drug carriers, triggering drug release [71]. This strategy ensures that drug

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release occurs intracellularly within cancer cells rather than in circulation.

IV. Enzyme-Triggered Drug Release

Certain tumor-associated enzymes (e.g., matrix metalloproteinases, cathepsins) can degrade specific peptide-based coatings on AuNPs, leading to controlled drug release [72].

B. External Stimuli (Externally Controlled Drug Release)

I. Temperature-Responsive Drug Release

Due to metabolic activity, tumors often exhibit higher temperatures (40–42°C) [73]. Thermo-responsive AuNPs are coated with heat-sensitive polymers (e.g., PNIPAM) that shrink at elevated temperatures, triggering drug release in tumor sites. Example: Gold nanoshells with thermosensitive coatings have been used for localized chemotherapy in lung cancer treatments.

II. Light-Triggered Drug Release (Photothermal & Photodynamic Therapy)

Gold nanoparticles absorb near-infrared (NIR) light, converting it into heat, destabilizing drug coatings or triggering drug activation [74]. This method is widely used in photothermal therapy (PTT) and photodynamic therapy (PDT). Example: Gold nanorods irradiated with NIR light have demonstrated enhanced chemotherapy and thermal ablation effects in glioblastoma models.

III. Magnetic and Ultrasound-Triggered Release

Gold nanocomposites with magnetic materials respond to external magnetic fields, aiding targeted delivery and controlled drug release [75]. Ultrasound waves can induce mechanical disruption of AuNP coatings, facilitating rapid drug release in deep-seated tumors. The advantages of stimuli-responsive AuNP-based drug delivery include improved drug targeting, controlled drug release, and combination therapy potential. Limitations and challenges include heterogeneity in tumor microenvironments: not all tumors exhibit uniform pH, enzyme expression, or redox conditions, affecting drug release efficiency [76]. Moreover, penetration issues are present as some stimuli (e.g., light, heat) may not effectively reach deep-seated tumors, requiring novel delivery strategies [77].

Gold Nanoparticles in the Treatment of Different Types of Cancer

Breast Cancer

Breast cancer is one of the most prevalent cancers worldwide, and the development of gold nanoparticle (AuNP)-based drug delivery systems have shown promising advancements in targeted therapy, reducing systemic toxicity, and improving treatment efficacy. Gold nanoparticles play a significant role in breast cancer treatment through chemotherapy enhancement, photothermal therapy, and targeted drug delivery.

5.1.1. Applications of Gold Nanoparticles in Breast Cancer Therapy

A. AuNP-Based Chemotherapy and Drug Delivery

Gold nanoparticles enhance drug solubility and bioavailability, allowing for better tumor penetration [78]. Targeted delivery: Functionalized AuNPs with specific ligands (e.g., folic acid, HER2 antibodies) enable selective accumulation in breast cancer cells, reducing side effects [76]. Example: Doxorubicin-loaded gold nanoparticles have shown increased cytotoxicity in breast cancer cells while minimizing cardiotoxicity [79].

B. Photothermal Therapy Using Gold Nanoparticles

Gold nanoparticles absorb near-infrared light, converting it into heat to destroy cancer cells without damaging surrounding healthy tissue [74]. Gold nanorods and nanoshells are commonly used for localized hyperthermia in breast tumors, often in combination with chemotherapy or Immunotherapy [80].

C. Combination Therapy: Chemotherapy + photothermal therapy + Immunotherapy

Gold nanoparticles facilitate combination therapies, increasing treatment efficacy [73]. Example: AuNPs conjugated with paclitaxel and heated via NIR light showed enhanced tumor suppression in preclinical breast cancer models [71].

5.1.2. Advantages of AuNP-Based Therapy in Breast Cancer

1. Improved Drug Targeting: Functionalized AuNPs deliver chemotherapy drugs specifically to breast cancer cells, reducing systemic toxicity.
2. Enhanced Tumor Penetration: AuNPs improve drug retention and uptake in tumor tissues.
3. Noninvasive Treatment: Photothermal therapy allows for targeted tumor ablation without surgery.
4. Combination Therapy Potential: Chemotherapy + PTT + Immunotherapy provides a multimodal treatment approach.

5.1.3. Limitations and Challenges

1. Tumor Heterogeneity: Breast cancer subtypes respond differently to AuNP-based treatments [81].
2. Nanoparticle Accumulation: Ensuring AuNP clearance to prevent long-term toxicity is still a concern [82].
3. Clinical Translation Barriers: Regulatory approvals and large-scale manufacturing pose challenges for commercialization [78].

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Table 1. Summary of the factors affecting Biocompatibility and Stability of Gold Nanoparticles

Factor	Impact on Biocompatibility	Impact on Stability
Size	- <5 nm: High cellular penetration, potential cytotoxicity, fast renal Clearance. - 10–50 nm: Optimal uptake, minimal toxicity. - >50 nm: Accumulation in liver and spleen, possible immune activation.	- Small AuNPs: Risk of aggregation if not stabilized. - Larger AuNPs: Longer circulation but higher immune system recognition.
Shape	- Spherical: Most stable and biocompatible. - Nanorods/Nanostars: Higher cellular uptake but may induce cytotoxic effects.	- Nanorods/Nanostars: More prone to aggregation without surface coating.
Surface Chemistry	- PEGylation: Reduces immune recognition and enhances circulation. - Polysaccharides (Dextran, Chitosan): Improve biodegradability. - Cationic AuNPs: Higher toxicity due to membrane disruption.	- PEGylation/Polysaccharide Coating: Prevents aggregation and increases stability. - Uncoated AuNPs: Aggregate in high-salt environments (e.g., blood plasma).
Protein Corona Formation	- Alters cellular uptake and toxicity profile. - Can enhance or reduce targeting efficiency.	- Stabilizes AuNPs but may affect targeting properties.
pH and Ionic Strength Sensitivity	- Affects interaction with tumor microenvironment.	- Risk of aggregation in high-salt environments unless coated.
Oxidative Stability	- Gold core is inert, but surface ligands (e.g., thiols) may degrade over time.	- Surface modification enhances long-term stability.
Toxicity Considerations	- Low dose (<10 μg/mL): Generally safe. - High dose (>50 μg/mL): Potential oxidative stress and inflammation.	- Controlled release strategies (e.g., pH-responsive coatings) improve safety.
Clearance Mechanisms	- Renal Clearance (<5 nm): Rapid elimination through urine. - Liver/Spleen Clearance (>10 nm): Removed via macrophages.	- Surface coatings (PEG, dextran, etc.) prolong circulation time and prevent rapid Clearance.

Table 2: Comparison of Passive and Active Targeting Strategies

Feature	Passive Targeting	Active Targeting
Selectivity	Low	High
Drug Accumulation	It relies on the EPR effect	Ligand-receptor interactions
Cellular Uptake	Limited	High
Complexity	Simple	More complex
Clinical Translation	Easier	More challenging

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Table 3: Summary of Clinical Trials on Gold Nanoparticle (AuNP)-Based Cancer Therapies.

Clinical Trial	Application	Cancer Type	Phase	Findings	Ref.
CYT-6091 (Aurimune)	TNF-α-conjugated AuNPs for targeted chemotherapy	Solid tumors	Phase I	Well-tolerated, enhanced tumor accumulation.	[83]
AuroLase Therapy (Nanospectra)	Photothermal ablation using AuNPs	Prostate cancer	Phase I/II	Effective tumor reduction with minimal side effects.	[84]
AuNPs for Radiation Enhancement	AuNPs to enhance radiotherapy	Head neck cancer	Phase I	Increased radiosensitization and improved patient outcomes.	[85]
AuNP-Based Imaging Agents	Gold nanoprobes for early tumor detection	Breast cancer	Phase II	Improved imaging resolution for tumor localization.	[86]

5.1.4. Future Directions

1. Personalized Nanomedicine: Tailoring AuNP-based treatments based on breast cancer subtype (HER2+, TNBC, etc.) for precision therapy.
2. Smart AuNP Drug Carriers: Development of stimuli-responsive nanoparticles that release drugs in response to tumor-specific conditions (pH, enzymes, temperature).
3. Clinical Trials and Regulatory Advances: Expanding FDA-approved AuNP-based therapies for breast cancer treatment.

Brain Cancer (Glioblastoma)

Glioblastoma (GBM) is one of the most aggressive and lethal brain tumors, characterized by rapid growth, high invasiveness, and resistance to conventional therapies. The presence of the blood-brain barrier (BBB) makes drug delivery to the brain highly challenging, limiting the effectiveness of chemotherapy and targeted therapies. Gold nanoparticles (AuNPs) have emerged as promising nanocarriers for drug delivery, enabling better BBB penetration, tumor targeting, and theranostic (therapy + diagnostic) applications. BBB is a highly selective endothelial layer that restricts most drugs from entering the brain. However, functionalized AuNPs have been developed to overcome this challenge through various mechanisms: Glioblastoma tumors have leaky vasculature, which allows nanoparticles to accumulate within tumor tissues [87]. PEGylated AuNPs improve circulation time, enhancing passive tumor accumulation [88].

Active Transport Strategies for BBB Penetration

1. Receptor-Mediated Transport (RMT)

Gold nanoparticles functionalized with transferrin or low-density lipoprotein (LDL) can bind to blood-brain barrier receptors, allowing active transport into the brain [89]. Example: Transferrin-coated AuNPs loaded with paclitaxel significantly improved drug penetration into GBM tumors [90].

2. Cell-Penetrating Peptide -Mediated Transport

Gold nanoparticles conjugated with cell-penetrating peptides (e.g., TAT peptide) enhance cellular uptake and blood-brain barrier penetration [91]. Example: TAT-functionalized AuNPs delivering siRNA to glioblastoma cells showed enhanced therapeutic effects.

3. Nanoparticle-Based Trojan Horse Approach

AuNPs can be encapsulated within macrophages or exosomes, allowing them to cross the BBB by mimicking natural biological transport mechanisms [92].

4. Magnetic and Ultrasound-Guided Delivery

Magnetic AuNPs (coated with iron oxide) can be directed across the BBB using external magnetic fields [93]. Focused ultrasound (FUS) combined with AuNPs creates temporary BBB openings, enabling enhanced nanoparticle delivery [94].

Theranostic Applications of Gold Nanoparticles in Glioblastoma

Theranostic is the combination of therapy and diagnostics in a single nanoparticle system. Gold nanoparticles are ideal for theranostic due to their:

1. Strong X-ray absorption properties (for CT imaging)
2. Surface plasmon resonance (for photothermal therapy)
3. High biocompatibility and functionalization potential

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Gold Nanoparticles for Imaging, Diagnosis and Glioblastoma Therapy

1. AuNP-Enhanced MRI and CT Imaging

Gold nanoparticles act as contrast agents, improving brain tumor imaging through computed tomography (CT) and magnetic resonance imaging (MRI) [95]. Example: Gold nanoclusters conjugated with gadolinium-enhanced GBM detection in MRI scans [96].

2. Fluorescence and Raman Imaging

Gold nanoshells conjugated with fluorescent dyes enable real-time visualization of tumor cells during surgery [97]. Example: SERS (Surface-Enhanced Raman Scattering)-labeled AuNPs improved intraoperative tumor margin detection.

3. Gold Nanoparticles for Glioblastoma Therapy

3.1. Photothermal Therapy with AuNPs

Gold nanorods absorb near-infrared light, converting it into heat to selectively destroy GBM cells [98]. Example: AuNP-based laser ablation therapy significantly reduced glioblastoma tumor volume in animal models.

3.2. Photodynamic Therapy (PDT) with AuNPs

When exposed to light, as conjugated with photosensitizers, generate reactive oxygen species (ROS), inducing glioblastoma cell apoptosis [99]—example: Gold nanocages loaded with porphyrins enhanced PDT efficacy in glioblastoma therapy.

3.3. AuNP-Based Chemotherapy and Drug Delivery

Gold nanoparticles can carry chemotherapeutic agents (e.g., temozolomide, paclitaxel) across the BBB, enhancing drug bioavailability [87]. Example: Doxorubicin-loaded AuNPs functionalized with transferrin improved drug delivery and reduced GBM tumor size.

Applications in tissue engineering and regenerative medicine

In tissue engineering and regenerative medicine, effectively monitoring biomaterial scaffolds, transplanted cells, differentiation status, angiogenesis, and healing mechanisms is essential yet difficult. Integrating AuNPs as labels and contrast agents enables novel opportunities for noninvasive, longitudinal observation of these dynamics. For instance, AuNP-loaded decellularized scaffolds were monitored by CT to evaluate in vivo breakdown. AuNPs have been utilized for prolonged photoacoustic monitoring of stem cell survival and differentiation within hydrogel constructions. They have been integrated into cell sheet engineering for simultaneous PA imaging and photothermal tissue adhesion. The integration into 3D bioprinted structures has facilitated visibility through CT and MRI. Gold nanoparticles (AuNPs) have been utilized for the spatial mapping of protease activity and pH levels within tissues through activatable SERS nanosensors. By enhancing signals from engineered tissues or activity-responsive probes, AuNPs offer novel methods for evaluating engraftment, maturation, and integration of regenerative therapies [100].

Clinical Trials and Regulatory Considerations

Gold nanoparticles (AuNPs) are at the forefront of nanomedicine research for cancer treatment. However, their clinical translation is hindered by safety concerns, regulatory challenges, and scalability issues. This section explores the current status of clinical trials, FDA/EMA regulations, and barriers to commercializing AuNP-based drug delivery systems. The clinical applications of AuNPs range from drug delivery to photothermal therapy (PTT) and imaging. Several clinical trials have been conducted to evaluate their efficacy and safety in treating various cancers, as depicted in Table 3. Most AuNP-based therapies have completed Phase I trials, demonstrating safety and biocompatibility. Phase II and III trials face large-scale production and long-term toxicity evaluation hurdles. Despite promising preclinical results, few AuNP-based therapies have reached late-stage clinical trials due to long-term toxicity concerns and variability in manufacturing and reproducibility.

Regulatory Framework for Nanomedicine

Both the FDA and EMA regulate nanoparticle-based therapies under existing pharmaceutical guidelines.

FDA Regulations (U.S.)

- AuNP-based therapies are classified as "combination products" (drug + device).
- The Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research oversees safety, efficacy, and stability studies.
- Clinical trials must follow Good Manufacturing and Laboratory Practices to ensure reproducibility.

EMA Regulations (Europe)

- The Committee for Medicinal Products for Human Use (CHMP) evaluates nanomedicines for therapeutic use.
- Comparability studies are required to assess batch-to-batch consistency.
- It requires approval from long-term pharmacokinetics and toxicology studies.

Conclusion

Gold nanoparticles hold great potential for transforming cancer therapy, offering targeted, efficient, and minimally

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invasive treatment options. However, addressing toxicity concerns, standardizing manufacturing, and navigating regulatory pathways will ensure their successful integration into clinical oncology. With continued research and innovation, AuNP-based cancer therapies could soon become a mainstay in modern medicine.

Ethical consideration

All the participants in this study gave their informed permission.

Conflicts of Interest

No conflicts of interest are disclosed.

The authors reported no potential conflict of interest.

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