Review

Recent Advances in Development of Gold Nanoparticles for Drug Delivery Systems

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Abstract: Nano particles are arguably used in the biomedical field. Cancer remains a significant public health threat. Gold nanoparticles (AuNPs) are a natural choice for treatment of cancer, due to their simplicity of preparation, their unique optical characteristics, stability, electronic structure, nanostructure, biocompatibility, flexibility in sensing and detection. AuNPs can be conjugated with all the human body's physiological mechanisms. Various nanomaterials strategies have been approached to increase tumor selectivity, therapeutic index, and anticancer activity, as the standard drug delivery method lacks proper distribution of chemotherapeutics given the complexity of the cancer cells. Recent studies have revealed that AuNPs can readily be modified to allow direct pharmaceutical drug delivery to the target tissue. AuNPs can also deliver their contents in response to external or internal stimuli after approaching their target site. Accordingly, we discussed advanced AuNPs features that showed great potential in improving precision treatments in both non-personalized and high accuracy applications and highlighted the in-depth role of nanotechnology-based medication delivery as well as the most difficult aspect of medicinal effectiveness and safety.

Keywords: bioavailability, physiological mechanisms, nanomaterials strategies, therapeutic index, target tissue, non-personalized, medicinal effectiveness

1 INTRODUCTION

Currently, the use of Nano science, as a new method in disease detection, management, and treatment, has received increasing attention in the biomedical area[1]. Nanotechnology with a nano scale from 10 to 1000nm in extent and covering the study of structural assets of nanoparticles, displays various distinct characteristics that differ significantly from those in microscopic particles or large materials[2]. The use of nanoparticles in a variety of industries, from oil and natural gas to cosmetics and nano science, has ushered in a new age, the nanoscale period. Current applications of nanotechnology are multidisciplinary, such as engineering, biology, chemistry, and physics, and it is biomedical uses contain liposomes,

graphene, quantum dots, polymeric nanoparticles, magnetic nanomaterials, carbon nanotubes, and metallic nanomaterials, which are attributed to their large definite surface, high antioxidant capability, great surface action, outstanding bioactivity, and suitability for molecular manipulations[3-7]. Nanotechnology may solve the restrictions of traditional delivery, ranging from large-scale problems like bio-distribution to small barriers like molecular drugs, through transmembrane targeting, chemical transfer to select organelles, and other related techniques, to make these promising nano-enabled technologies more attainable and clinically applicable[8]. Nanotechnology-based therapeutic agents are being developed as an alternate technique, by modifying the physicochemical properties of antiviral medications to enhance treatment efficiency. However, when it comes to the effectiveness and safety profile of nanotechnology-integrated nano-medicines, there are still many crucial elements to consider, such as immunogenicity, target selectivity, and biocompatibility. Viruses, on either, have had a different technique for evading cell-mediated immune responses for millions of years[9]. Some of these stealthy capabilities are characterized by viral physiochemical properties such as size, shape, hydrophobicity, and surface charge. Gold nanoparticles (AuNPs) are an excellent study material because they're one of the most resistant to oxidation in the physiological environment (strong ionic strength, incl., temperature and variable pH), non-toxic, distinct surface effect, and easy to synthesis. A broad range of chemical methods has been established to generate AuNPs with manageable form and structure, as well as the occurrence of surface plasmon resonances, which have displayed remarkable phenomena such as different kinds of arrangement and quantum effects. AuNPs are heterogeneous nanomedicines that have been widely used in cancer therapies, including gene therapy, chemotherapy, photothermal therapy, and radiotherapy, as well as genetic imaging, biosensors, and drug transporters[10-13]. Due to the negative charge of AuNPs, particles can be easily functionalized by a variety of proteins and their noticeable optical and electronic properties[14-17]. Furthermore, biodegradable surface covering can be applied to the NP surface to ensure stability under physiological conditions[18,19]. Surface chemistry allows functional ligands to be coated on NPs, allowing them to perform several biological tasks at the molecular or functional levels simultaneously. AuNPs have been used since the Middle Ages, and they have been referred to as potable gold[16]. AuNPs have a high x-ray absorption coefficient, surface plasmon resonance, and radioactivity, which contribute to their clinical applications[20-22]. Other physiochemical features/functionalities, including magnetism, stimulation, anti-fouling, and cell targeting, can be introduced by integrating other nanostructures onto AuNPs[23-25]. Various approaches allow the cellular uptake and internalization of AuNPs, which are subject to several parameters, such as particle size, surface characteristics, morphology, and functionalization. AuNPs can be ingested via passive absorption, cytosis, binding site endocytosis, transcytosis, or non-specific receptor-independent endocytosis, depending on these characteristics[26-28]. Nanoparticles can be coupled to drugs or other substances and targeted passively or actively. The nanomaterials are connected to ligands such as peptides or chemotherapy drugs in active targeting. The enhanced permeability and retention (EPR) outcome enable broad permeability of the tumor circulation and convenient aggregation of nanoparticle in the tumor in passive targeting[28,29]. Physical absorption and ionic or covalent interaction allow direct linkage of some medicinal substances to gold nanoparticles[30]. This study will concentrate on the most recent research on how AuNPs can be used in molecular imaging and as drug carriers for disease therapy.

2 AuNPs AS DRUG DELIVERY CARRIERS

The invention of AuNPs has unfolded a world of potentialities for selective medication delivery. AuNPs have shown great potential as drug delivery vehicles. AuNPs, with a range of targeting ligands, are considered an optimal carrier for targeted medication delivery of each novel and established metastatic tumor medicine[31]. Exploitation poly antifreeze (PEG) as a spacer increases the surface of AuNPs. The amphiphilic properties of polymers provide high stability of AuNPs in physiological circumstances and permit mixtures on AuNPs. The interactions between the binding teams upon this small and the numerous proteins in motion facilitate the rapid approval of these carriers by Ref[32]. AuNPs deliver therapeutic molecules into their targets, such as mixture proteins, DNA, and vaccines, which will manage the unleash of the drug exploitation by internal or external mechanisms. Antibiotics and alternative therapeutic compounds directly mix with AuNPs through physical absorption by valence or ionic bonding. Researchers developed a substance shield/deshield technique supported by the pH scale-responsive AuNPs with ultrasharp pH sensitivity[33]. Immunosuppressant could be a vitamin B complex Analog that inhibits neoplastic cell growth and replica and is often used as a metastatic tumor medication[34]. The combination of immunosuppressant (MTX) with AuNPs, features incontestably higher toxicity and neoplasm cell proliferation than its single use. The chemicals on the immunosuppressant molecules will bond to the surface of AuNPs upon an immediate incubation. In an in vitro study, antibiotic (DOX) conjugated to pH-sensitive linker-coated AuNPs via an acid-labile linkage showed incontestably higher drug accretion than free DOX in multidrug-resistant MCF-7/ADR cancer cells. This way of DOX-AuNPs interaction permits for protoplasm evoked DOX secretion from the AuNPs once inside acidic organelles. (Figure 1) With its excellent biocompatibility, rapid clearance from blood circulation, and enhanced tumor retention, small AuNPs have attracted much attention in
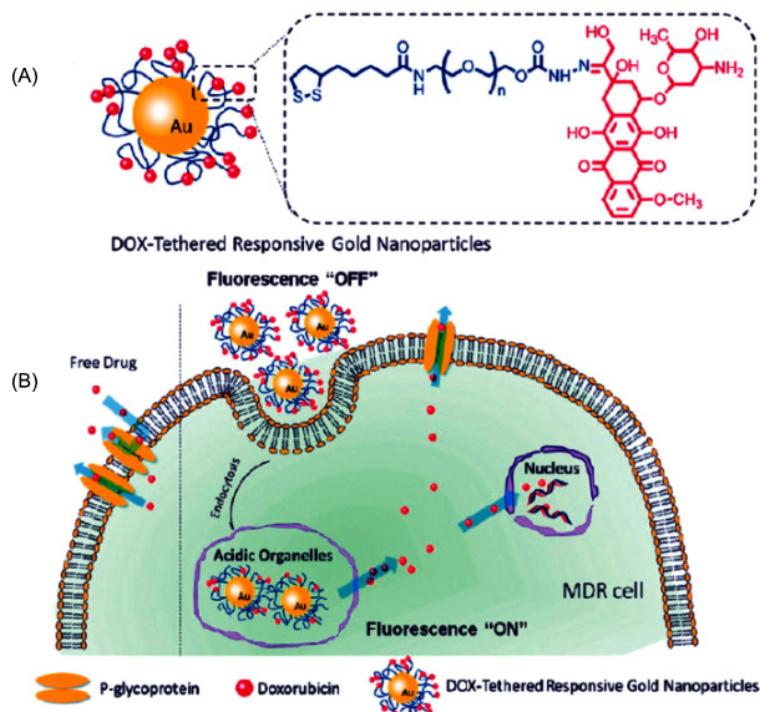
Figure 1. A Schematic illustration of DOX-tethered responsive gold nanoparticles (AuNPs); B Schematic illustration of the cooperation between enhanced DOX cellular entry and a responsive intracellular release of DOX into the cells to overcome drug resistance.
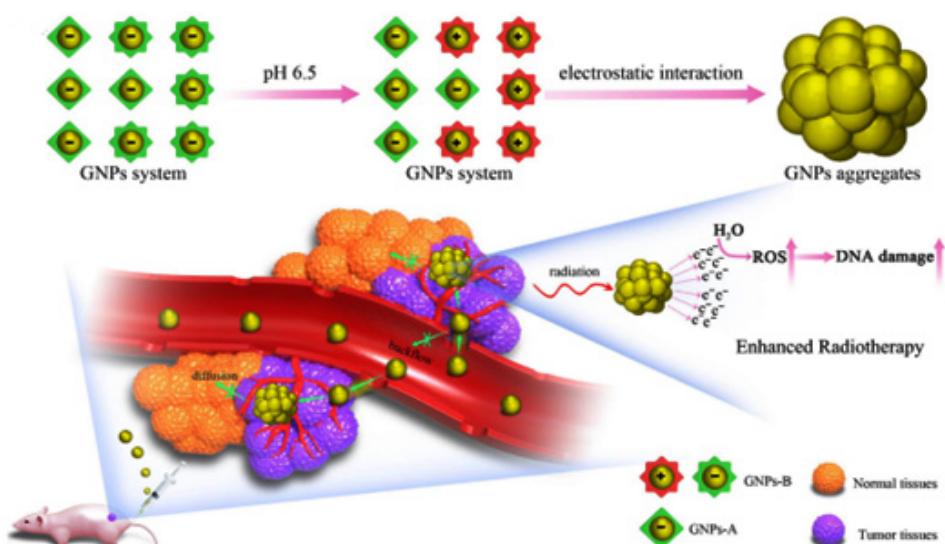
Figure 2. Diagram depicting the acid-triggered aggregation and composition of AuNPs system and schematic illustrations of in vivo behavior of AuNPs system after intravenous injection for increased tumor retention and enhanced RT.

radiosensitization. Liu's group reported to utilize small-sized AuNPs, that aggregate upon an acid trigger, as radiosensitizers in tumor RT (Figure 2)[35].

As a result, the toxicity of DOX was improved with the employment of this model of delivery mechanism[36,37]. Another in vitro investigation found that oxaliplatin combined with polymer-modified AuNPs had stronger toxicity than free oxaliplatin in HT29, HCT15, and RKO human carcinoma cell lines, also as accrued drug carriers[38,39]. Researchers used chitosan-capped AuNPs (CS-GNPs) with RGD as a carrier for Sunitinib (STB) to the growth vasculature in another in vitro study. With a similar drug dose, RGD-STBCS-AuNPs were a lot of venturous to cells than free STB, indicating that the created nanoparticles improved distribution and clearance by cells[40]. We now focus on first-generation chemotherapeutic agents. Due to their toxicity, researchers' attention has been caught by conjugating them to GNPs with the aim of reducing the doses and consequently the side effects Table 1. This association leads to smart solution stability and high animate thing transit potency, each of that is notably helpful for transport to the nucleus[41].

Table 1. Variety of Applications of AuGNs in Drug Delivery of 1st Generation Anticancer Drugs[42,43]

Anticancer Drug	Cancer Cells	Form of Nanoparticle	Major Test Outcomes
Oxaliplatin (OPT)	Lung and colon cancer cells	OPT-PEG-Carb-GNP	Higher cytotoxicity than oxaliplatin in HCT15, HT29, and RKO human colon cancer cell lines
Methotrexate (MTX)	LL2 cells	MTX-GNP	Higher cytotoxicity and higher accumulation in tumor cells and better tumor inhibition than free MTX
Gemcitabine (GMC)	PDAC cell lines	GMCplectin-1-targeting peptide-GNP	More cytotoxicity in vitro and more antitumor effect in vivo
Etoposide (ETP)	NCI-H69 cell line	ETP-HPMC/PVAGNP	Improved cytotoxicity compared to free etoposide
Doxorubicin (DOX)	Multidrug-resistant MCF-7/ADR cancer cells	DOX-PEG-GNP with acid-labile linkage	Better drug accumulation and enhanced cytotoxicity comparing to free DOX
6-mercaptopurine (6-MP)	K-562 leukemia cells	6-MP-GNP	Enhanced antiproliferative effect compared to 6-MP administered alone
Bleomycin (BLM)	MDA MB231 cells	BLM-RGD-GNP	More DNA damage and less survival than free BLM

3 AuNPs FOR GENE DELIVERY

Gene therapy has emerged as a viable option for treating and preventing illnesses that are beyond the scope of standard approaches[44-46]. Viruses can also be used to deliver highly effective gene therapy[47]. However, the demand for an effective and nontoxic gene therapy delivery mechanism remains unmet. Similarly, the usefulness of non-viral gene delivery techniques has yet to be proven[48]. An effective delivery vehicle should be able to enter the cell quickly, shield nucleic acid from nuclease destruction, and keep nucleic acid in a functional system within the nucleus[49]. Recent research has revealed their therapeutic effects and capabilities of delivering various types of oligonucleotides, including single-stranded RNA, double-stranded DNA, plasmids, and single-stranded DNA. Nucleic acid is protected by AuNPs with a variety of morphologies, such as nanospheres and nanorods, and is not degraded by nuclease. In gene delivery and gene therapy, oligonucleotide and siRNA-modified AuNPs conjugates are used as intracellular gene regulation agents that can activate immune-associated genes[50-52]. Non-covalent and covalent interactions can be used to link AuNPs to oligonucleotides. These findings are critical for translational research and the advancement of gene and treatment delivery technologies using oligonucleotide-modified AuNPs conjugates[52]. So far, gold-thiol conjugation or the usage of electrostatic incorporated into the plasmid DNA has been proposed as methods for loading oligonucleotides to AuNPs. The results showed that the composite particle could protect DNA from enzymatic degradation and control T7 RNA polymerase DNA transcription[53-56]. In gene silencing applications, Mirkin et al. used citrate-stabilized spherical AuNPs coated with a dense layer of single-stranded DNA molecules functionalized with single or multiple thiol groups (Figure 3)[57]. The particle complexes were created with a consistent target cell for the correct nucleotide sequence and a 99 percent higher cellular internalization rate without cytotoxicity. When preserved with DNAs, certain antisense oligonucleotides decomposed at a far slower rate in AuNPs than in free antisense oligonucleotide duplexes[57].

The resulting conjugate was resistant to enzyme breakdown and had a high level of cellular internalization[58]. Fitting nucleic acids and auxiliary components such as PEG and polyetherimide to the surface of AuNPs, on the other hand, causes ineffective nucleic acid release at desired sites. The capacity of gold clusters shielded by various monolayers functionalized with quaternary ammonium salts to transfect plasmid DNA was proven. The incorporation of paired DNA with grafted single-stranded DNA was enhanced, and the results revealed that numerous parameters, including DNA, AuNPs, and hydrophobicity, contribute to effective transfection meetings[59,60]. The findings also demonstrate the potential of AuNPs as innovative carriers for delivering genes into neuron cells. Zhao et al. improved Au NR-based nano-carriers by adding poly-sodium 4-styrenesulfonate and poly-allylamine hydrochloride, enabling their delivering small interfering RNA against LSD1 to induce differentiation in human mesenchymal stem cells[60]. This study's findings could help with tissue regeneration therapy by introducing tiny interfering RNA. By functionalizing AuNPs with amino acids, an efficient scaffold for attaching gold colloids to DNA can be created[61]. When compared to poly-lysine, AuNPs functionalized with lysine dendron have been shown to be 28-fold more effective in gene expression[62].
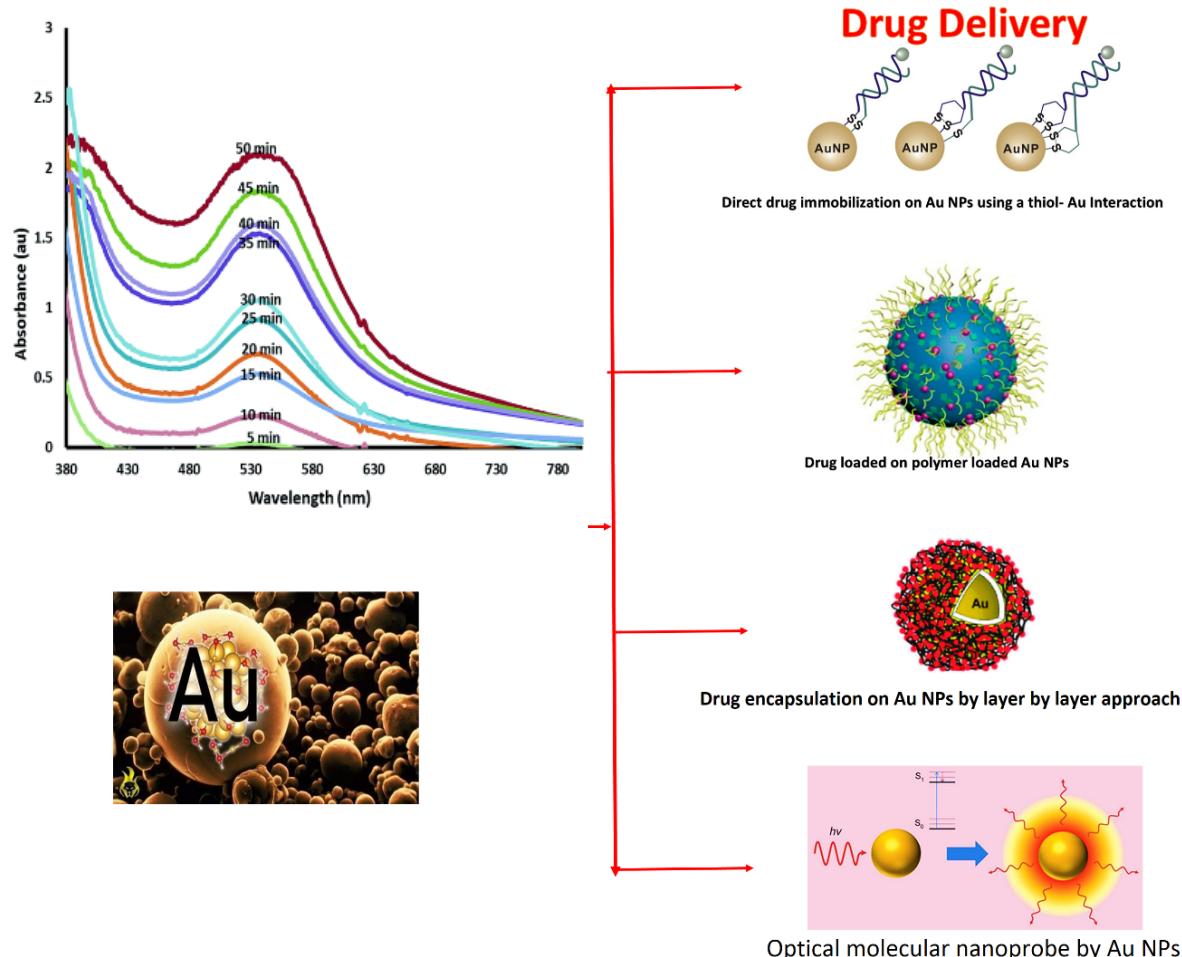
Figure 3. A schematic illustration of AuNPs based drug delivery and molecular diagnostics. AuNPs provide large surface areas for versatile surface modifications and show unique optical properties suitable for molecular sensing and diagnostics.

The transport of antisense DNAs to the nucleus for controlling alternative splicing of pre-mRNA of diseaserelated genes is an appealing technique for gene therapy[63-65]. Such pH-responsive AuNPs coated with layers of binding materials are promising for increased DNA governed by the terms. Acid-sensitive AuNPs feature great potential for delivering DNAs besides mRNA alternative splicing suppression given the easy modification of AuNPs with DNAs.

4 AuNPs FOR PROTEIN DELIVERY

Certain proteins and peptides can be carried by AuNPs as nanocarriers. Protein-AuNPs interfacial interactions have important implications for AuNPs applications in biology and therapeutics[66]. In a previous study, chitosan-functionalized gold nanoparticles were employed to transport insulin. Chi-tosan is a non-toxic biopolymer that is utilized to produce and stabilize the nanoparticles. Insulin adsorbs strongly on the surface of chitosan-coated particles, making them useful for transmucosal administration. Cationic tetraalkylammonium functionalized AuNPs,

according to Verma et al[66], by complementary electrostatic interaction, identify the surface of an anionic protein and inhibit its activity, which can be reversed by cellular glutathione concentrations. Treatment of protein-particle complex with SH boosted its activity and thereafter resulted in the release of free protein, indicating AuNPs as potential protein transporters. Krol et al. coupled AuNPs with cell penetrating peptides and looked for lysosome sorting peptides potentially available to selectively localize lysosomes. When opposed to citrate-stabilized AuNPs, protein conju-gation significantly reduced AuNPs retention in the liver, according to their studies (Table 2). We summarize recently published literature related to the regulation of protein binding by AuNPs' surface charge, hydrophobicity, and combinatorial surface modifications, which are generally considered as important factors that characterize AuNPs' surface coating. This research demonstrates that sustained conjugation improves the effectiveness and specificity of AuNPs in target organs, implying a potential use in nanopharmacology and nanomedicine[67,68].

**Table 2. Protein Binding Regulated by AuNPs' Surface Chemistry**

	AuNPs		
Size	Protein Binding Capacity	Zeta Potential	Ref
5nm	Citric-,phosphine-, poly (isobutylene-alt-maleic	PEG, citric-, phosphine-, poly(isobutylene-alt-maleic anhydride)	[69]
15, 30, 60 , 90nm	Negatively correlated with PEG density	PEG (5 kDa)	[70]
13nm	Tannic acid>PEG	PEG (−13.5 mV), tannic acid (−28.1 mV)	[71]
14-22nm	Mercaptosuccinic acid and N-4-thiobutyroil	Mercaptosuccinic acid, N-4-thiobutyroil glucosamine, PEG5000 and alkyl-PEG600	[72]
5-20nm	PAEA>PAA>PDHA	Poly (N-(2-aminoethyl) acrylamide) (PAEA, 46-57 mV), poly (acrylic acid) (PAA, -25 to -60 mV), poly (N-(2,3-dihydroxypropyl) acrylamide) (PDHA, slightly negatively charged)	[73]
45nm	Positively correlated with PEG chain length	PEG (2, 5, 10, 20 kDa), -5.4 mV to -25.4 mV	[74]
1.55nm	14-3-3 protein-binding peptide derived from CRaf	The thiol group of this cysteine	[75]
10, 14, 40nm	Glycosylated vs nonglyco-sylated transferrin	Glutathione (GSH), citrate, PEG	[76]

## 5 AuNPs ACTIVE TARGETING TO CANCER CELLS

Photothermal therapy (PTT) is a type of cancer treatment in which nanoparticles (NPs) are lodged in the tumor and generate heat in response to external laser light. The anti-angiogenic activity, photothermal action, and targeted drug delivery of AuNPs mediated cancer therapy were investigated in vitro and in animal models. AuNPs are also widely used only for PTT due to their various superior synthesis, bioactivity, simple Au thiol functionalization chemistry for the connection of desired particles, a simple diameter that enables tumor absorption, effective light to heat transformation, and ability to handle near infrared light, which absorbs tissue greater depth than some other light wavelengths[77-81]. PTT is used in combination with other medications. Available chemotherapeutics act in diverse places with various modalities, in which some function in the nucleus to break DNA (doxorubicin, platinum medicines), while others work in the cytoplasm or affect organelles such as the mitochondria[82]. In both the NIR-I and NIR-II, multifunctional plasmonic NPs with highly efficient surface-enhanced Raman scattering (SERS) imaging and NIR light-triggered plasmonic photothermal treatment of cancer cells were investigated[83]. Another study found that AuNPs' ability to bind to quercetin inhibited epithelial-mesenchymal transformation, gene expression, and potential complications of breast cancer cells by attacking the epidermal growth factor receptor/vascular epithelial growth factor receptor-2 (EGFR/VEGFR-2) signal transduction pathway, suggesting that AuNPs improved the benefits of quercetin[78]. Such multifunctional nano-stars offer tremendous promise in SERS mapping and a wide spectrum of light-mediated applications, according to in vitro investigations on A549 human lung adenocarcinoma cells[84]. Using the 6 MV FFF (Figure 4A) and FF (Figure 4B) photon beams, Figure 4 demonstrates the dependences of dose enhancement factor (DER) vs AuNPs concentration for various prostate diameters. In an attempt to maximize both properties, NPs with detachable stealth corona systems and charge-reversal systems (negative or neutral charge for circulation, positive charge for absorption) have recently been designed[85,86]. One such approach binds PEG to the surface of the NP using an MMP-degradable linker; in the tumor environment, the PEG coating degrades, revealing a cell-penetrating peptide. These cleavable PEG-lipids have corresponding fracture mechanisms, so their application can achieve long-term circulation and promote drug absorption at a specific location.The cleavable mechanisms are shown in the Figure 5[86,87].

Research approaches enhance AuNPs drug delivery using tumour-targeting moieties, and so increase the efficacy of PDT have been summarised in Table 3. AuNPs can potentially be utilized in cancer radiation as a dosage booster. If AuNPs are given to a patient, dosage augmentation at the tumor can boost cancer cell death while preserving the surrounding vital tissues.
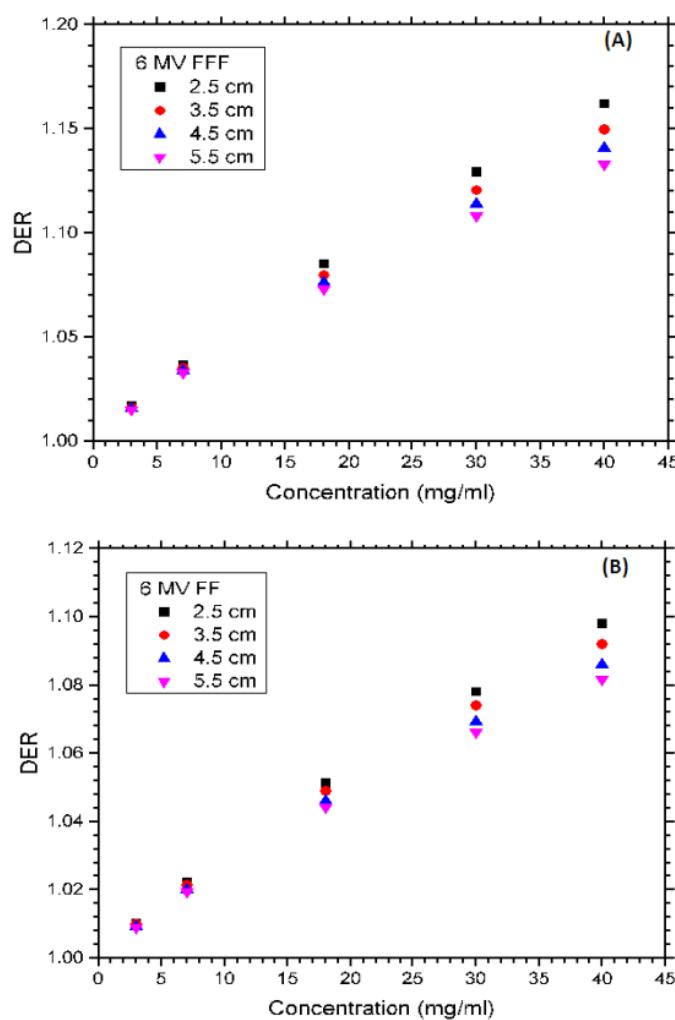
Figure 4. Relationship of the DER and AuNPs concentrations, varying with different prostate sizes in the phantom using the 6 MV (A) FFF and (B) FF photon beams. AuNPs with concentrations equal to 3, 7, 18, 30, and 40 mg/ml were used. The DER was calculated as the ratio of the target dose with NP addition to the target dose without NP addition. Reprinted with permission from Ref[68].
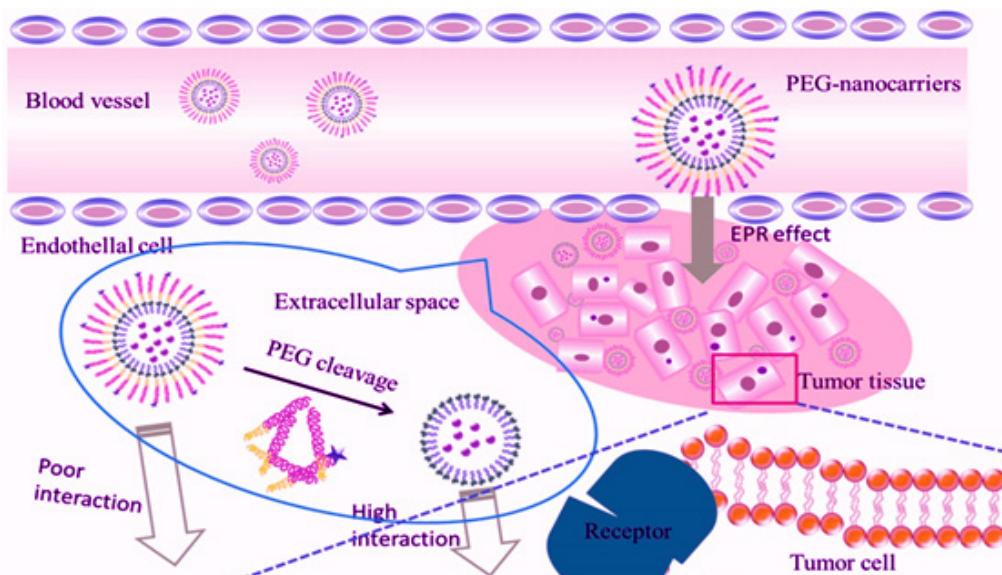
Figure 5. The bonds are cleaved and the cleavable mechanisms in the target site. Reprinted with permission from Ref[86].

Table 3. Targeting Moiety Approaches Used to Enhance AuNPs Active Drug Delivery Systems in Tumours

NP	Targeting Moiety	PS	Direct or Indirect Targeting	Tumour Overexpression Receptor	Study Type	Cancer Cell Line or Tumour Model	Results	Ref
Au	mAB	Porphyrin	Direct	erbB2 receptors SK-BR-3	In vitro	Human breast cancer cells	Monophasic method NP PS elicited targeted PDT	[88]
PEG-Au	mAB	Zinc phthalocyanine derivative (C11Pc)	Direct	HER2 receptor	In vitro	Breast carcinoma cell lines (SK-BR-3 & MDA-MB-231)	Enhanced efficacy of PDT cell death when tumour-associated antigens were present on malignant cells	[89]
Au	mAB	Silicon phthalocyanine PC 4	Direct	Prostate-specific membrane antigen (PSMA-1)	In vitro & in vivo	Prostate cancer PC3pip cell line & xenografted mice	Nanodrug system enhanced uptake four fold, with significant cell death & tumours remained in remission 14 days post PDT	[90]
PEG-Au	mAB & Peptide	Zinc phthalocyanine photosensitiser (C11Pc)	Direct	HER2 receptor or jacalin, a lectin specific for carbohydrate T anitigen	In vitro	HT-29 colorectal adenocarcinoma cells & SK-BR-3 breast adenocarcinoma cells	Both T antigen & overexpressed HER-2 reported enhanced targeted PDT with 80-90% in HT-29 cells & >99% in SK-BR-3 cells	[91]
Au	DNA Aptamer	Chlorin e6	Direct	Specific targeting aptamers-TLS11a	In vitro & in vivo	HepG2 Hepatocellular carcinoma cell line xenograph mouse model	Programmable synergistic, targeted PDT, with hypoxia-activated chemotherapy treatment for hepatocellular carcinoma	[92]
Au nanorod	DNA Aptamer	Chlorin e6	Direct	Sgc8 leukemia aptamer, which can specifically bind to protein tyrosine kinase 7 (PTK7) receptor	In vitro & in vivo	CEM (CCL-119, T-cell line, human & Ramos (CRL-1596, B-cell line, human Burkitt's lymphoma)	Enhanced uptake & targeting, with notable PDT & photothermal cell destruction	[93]
Au acrylic copolymer with imidazole groups	Folic acid	Spiropyran (SP)	Direct	Folic acid receptor	In vitro	Rat brain C6 glioma cancer cell line	71.8% improved cellular uptake & enhanced tumour targeted PDT	[94]
Au	Folic acid	Protoporphyrin IX (PpIX)	Direct	Folic acid receptor	In vitro	Human cervical carcinoma (HeLa) cells	Enhanced drug delivery & phototoxic properties	[95]
PEG-Au	Peptide	Silicon phthalocyanine PC 4	Direct & Indirect	EGF peptide (YHWYGYTPQNVIamide)	In vitro & in vivo	E29 rat glioma cancer cell line & tumour mouse model	Drug conjugate enhanced PS delivery, as well as enhanced PDT therapeutic efficacy two-fold	[96]
Au	Peptide Lactose	Zinc phthalocyanine	Direct & Indirect	Galectin-1 receptor	In vitro	Human breast MCF-7 cell line	Enhanced uptake, excellent ROS generation & efficient PDT	[97]

6 AuNPs-BASED MOLECULAR IMAGING

The rapid advancement of medical imaging technology in the past decade, offers physiological and pathological data with high sensitivity and specificity for wellness identification. Ultrasound imaging, Optical imaging, magnetic resonance imaging (MRI), and computed tomography (CT) have all shown great relevance as therapeutic probes for molecular imaging in the treatment of cancer. However, imaging contrasts and tracers, which are frequently utilized in clinical settings, have intrinsic limits and drawbacks. Nanotechnologies have increased cancer detection in vivo and increased the effectiveness of cancer targeting. Because of its diagnostic capabilities, effectiveness as a drug delivery vehicle, and ability to monitor patient response to therapy, the resulting nanosystem demonstrates significant potential in the rise of customized medicine[35]. AuNPs have piqued interest as therapeutic probes for molecular imaging in cancer treatment. The ability to create hybrid nanoparticles that can be targeted to vascular, extracellular, or cell surface receptors will be critical to any therapeutic improvements in nanoparticle-based therapy. This popularity has resulted in a plethora of AuNPs designs that differ in size, shape, surface modification, molecular, and physical properties. As a result, AuNP-based molecular imaging probes enable the use of CT, fluorescence, and other forms of optical imaging, photo acoustic imaging (PAI), MRI, and other new approaches. AuNPs with distinct genetic, biochemical, and chemical properties, constitute an excellent candidate for CT contrast agents that enable high sensitivity and spatial resolution detection and imaging of physiological processes[98]. The contradictory outcomes in different papers about the size impacts of AuNPs on CT imaging could be ascribed to the different approaches used. Because of their photodynamic transfer capabilities, AuNPs can be employed as PA imaging and photothermal imaging probes with near-infrared laser irradiation. Au nanorods, in particular, have a better photodynamic film thickness than AuNPs, which yields a considerably stronger imaging effect in PA imaging due to their higher absorption in the near-infrared region[99-101]. To boost the optical efficiency of AuNPs, novel solutions based on the particular environment of tumor sites require further development.

7 AuNPs TO IMPROVE HIV DRUG DELIVERY

Antiretroviral therapy (ART) has contributed to prolonged survival and a better quality of life pf HIV-1 patients. ART, however, is rather circumscribed in various aspects, including the cell transformation and poor penetration of specific anatomic compartments[102], for which enhancement on antiretroviral drug delivery is required to offset the insufficiencies. Inorganic gold crystals with a diameter of two to ten nanometers are used as a foundation framework for mixing molecules with different surface properties[103]. We show that an HIV integrase inhibition linked to an AuNPs may enter a variety of cell types, has antiviral activity, and can safely permeate the brain in vivo. In this work, AuNPs are found to be a positive option for HIV therapy. 4', 6-diamidino-2-phenylindole or Hoechst 33342 were used to identify the nuclei (blue)[102-104]. A transmittance overlay, Cell Mask stain, or-catenin stain is used to reveal the delineated plasma membrane for each cell type (green). Peripheral blood mononuclear cells were supplied by a donor cell. The viable population was selected by FACS analysis to measure cell-associated fluorescence (Figure 6). The accompanying fluorescence increased steadily over time, and it was likewise concentration-dependent. In conclusion, we have shown that small molecule-conjugated AuNPs may be delivered into cell types where HIV can multiply and that it has an antiviral effect in HIV-infected primary lymphocytes. In an in vivo model, we have also proven the delivery of gold particles into the CNS, notwithstanding a substandard entry. Because the transport of several therapeutic moieties on a single nanoparticle is technically achievable, this opens up significant future potential for the translational development of this technology. Antiviral particles including CNS-targeting compounds, as well as other molecules with unique or valuable functions, could be developed in the future[102-105].

8 LIMITATIONS OF AuNPs IN DRUG DELIVERY

While AuNPs present a bright future in pharmaceutical distribution, their defects, especially their possible negative effects deserve more attention in future studies. Although various studies have addressed many of the concerns about gold nanoparticles in biological applications, the conclusions completely contradict one another, and definitive answers to all of the questions about biocompatibility, biodistribution, retention, cytotoxicity, besides clearance time are still required. AuNPs non-specific targeting and potential to stimulate the host's immune system are two main drawbacks in medication delivery. Coating AuNPs with PEG covers their surface However, this perfect of the surface could result in toxic side effects. It's also critical to consider the method through which conjugated ligands can modify pharmacokinetics, bioavailability, and subsequently potential adverse effects. Specific types of ligands can be responsible for some toxicity. In-vitro toxicity, for example, has only been described for cationic ligands[106]. Additionally, because of drug resistance and the genetic variation of cancer cells, not all medicines will be effective for all patients. By coating nanoparticles with stromal antagonists, the efficacy of nano cancer medication carriers can be improved. However, to provide more precisely targeted nano therapeutics, more research is needed to find new molecular targets that are uniquely expressed in the cancer microenvironment. Targeting stromal cells could be one method to alleviate the problem of cancer heterogeneity. Cancer stem cells are another promising target for active drugs (CSC).
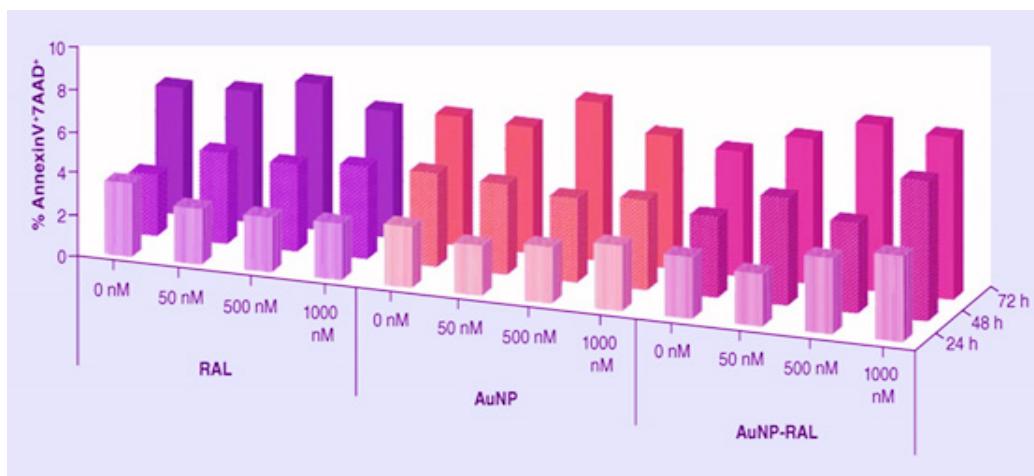
Figure 6. Cell viability measured by FACS after 24, 48, and 72h incubation with raltegravir, gold nanoparticle, or gold nanoparticle-raltegravir at different concentrations (0, 50, 500, and 1000 nm). Reprinted with permission from Ref[102].

Eliminating chemo resistance of CSCs could be a way for eradicating chemo resistance of cancer cells[107]. As a result, a variety of key difficulties, including effective formulation assays, long-term side effects, and cellular and immunological reactions, must be addressed, which needs additional research into the development of the aforementioned methodologies, particularly in terms of active targeting[108].

9 CONCLUSION

AuNPs demonstrate great potential in cancer therapy and drug delivery, as well as biodiagnostic and imaging. In spite of these advancements, the properties of AuNPs, such as long-term toxicity, stability, and immune response effects, high surface-to-volume ratio, surface versatility, low inherent toxicity, biocompatibility, optical properties, and ability to easily functionalize with biomolecules to achieve the desired selectivity, deserve further exploration. Moreover, AuNPs offer tremendous antiviral therapeutic potential by overwhelming the challenges of therapy resistance, low solubility, excellent intrinsic properties release, and short retention time of drugs in the plasm, etc. All of the conjugation or modification strategies utilized require thorough consideration. It would also be crucial to balance the contradicting elements of generating more effective acid-responsive AuNPs, such as expected targeting delivery versus undesirable nonspecific protein adsorption, to build a more effective acid-responsive AuNPs system. To facilitate the loading of the medication and biomolecules, diverse moieties, including PEG, amino acids and peptides, oligonucleotides, and antibodies, can be used to tune the surface of AuNPs. PEGlyation of AuNPs is the ideal choice of surface modification for in vivo distribution of therapeutic pharmaceuticals in light of its biocompatibility and facilitation of the escape of nano drug carriers from the body's immune system. Many in vitro and in vivo investigations have identified the promising

toxicity of AuNPs, including the loss of AuNPs' ability to cooperate with the target receptor, which can be facilitated by adorning the surface of AuNPs with target binding sites, nonbiodegradability, and toxicity. As a result, more research is needed to resolve toxicity concerns by defining the most appropriate combination with AuNPs properties for therapeutic agents. To summarize, smart AuNPs are a potential method given their advances in chemotherapy, RT, and PTT, but in vivo delivery effectiveness and clinical investigations are still needed.

Conflicts of Interest
These authors declared no conflict of interest.

Author Contribution
Abu-Dief AM planned for the idea and made the revision of the review article; Salaheldeen M revised the language of the article; El-Dabea T collected the data required for writing draft of revew article and adjusted the article according journal formatting; all authors approved the final version.

Abbreviation List
AuNPs, Gold nanoparticles
ART, Antiretroviral therapy
BLM, Bleomycin
CS-GNPs, Chitosan-capped AuNPs
CSC, Cancer stem cells
DOX, Doxorubicin
DER, Dose enhancement factor
EPR, Enhanced permeability and retention
ETP, Etoposide
GMC, Gemcitabine
MTX, Methotrexate

MR, Resonance imaging
OPT, Oxaliplatin
PEG, Polyethylene glycol
PTT, Photothermal therapy
PAI, Photo acoustic imaging
STB, Sunitinib
SERS, Surface-enhanced raman scattering
6-MP, 6-mercaptopurine

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